

Recent advances in alkylidene carbene chemistry

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Recent advances in alkylidene carbene chemistry

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1. Introduction

Alkylidene carbenes, also known as alkenylidenes, are reactive intermediates in organic chemistry. Their high reactivity

necessitates generation and trapping in situ, but unlike many carbenes,¹ they display high levels of selectivity without the need to be associated with a metal catalyst. Indeed, although many methods for the formation of alkylidene carbenes are metal-based, their reactivity is generally rationalized without invoking a role for the metal.

The most common reactions of alkylidene carbenes are shown below (Scheme 1). 1,2-Migration is the preferred reaction pathway for phenyl and hydrogen substituted alkylidene carbenes (Eq. 1). Since alkylidene carbenes precursors are often derived

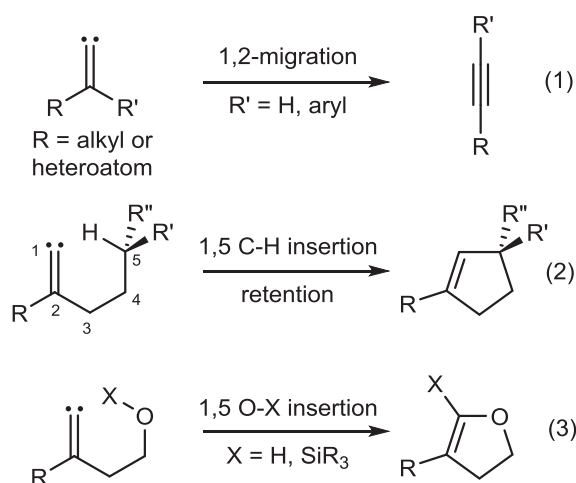
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from aldehydes and ketones, this offers a method of carbon homologation, and is extensively utilized in organic synthesis. Alkyl-substituted alkylidene carbenes generally undergo insertion rather than migration. Intramolecularly, this leads to cyclopentenes through a highly regioselective 1,5 C–H insertion reaction (Eq. 2). This reaction occurs with high levels of chemoselectivity (for more highly substituted C–H bonds) and is stereospecific (retention of absolute configuration at the insertion site), the latter process being consistent with alkylidene carbenes reacting through the singlet state. Coupled with the ability to insert into unfunctionalized C–H bonds, thereby simplifying structural complexity in the starting material, the 1,5 C–H insertion reaction of alkylidene carbenes is particularly useful in organic synthesis. Five-membered unsaturated heterocycle formation occurs when a heteroatom is present in the connecting chain, and is also observed in formal 1,5 insertions into heteroatom bonds, most commonly O–H and O–SiR₃, to make dihydrofurans (Eq. 3).



This review covers synthetic aspects of both the generation and reactions of alkylidene carbenes, including related organometallic chemistry, which fits into the reactivity patterns shown above. Other reaction pathways and factors affecting selectivity are also discussed, as are applications in target synthesis. Aspects of the chemistry of alkylidene carbenes have been previously reviewed in the literature. A short review on the synthetic potential of alkylidene carbenes appeared in 1997.² A comprehensive review by Knorr in 2004 concentrated on the evidence for alkylidene carbenes in a number of reactions.³ The use of hypervalent alkynyl iodides as precursors to alkylidene carbenes has been previously reviewed,⁴ as has the use of α -heteroatom substituted alkenyl lithium reagents.⁵ A 2010 review by Koskinen discussed developments in the conversion of carbonyl compounds to alkynes,⁶ and as such, the synthetic utility of this transformation will not be extensively covered.

2. Structure and bonding

In alkylidene carbenes, the carbenic centre is located on the terminus of a carbon–carbon double bond. Ab initio studies have shown that the carbenic carbon is effectively sp hybridized and exists in a singlet state **1** (Fig. 1) with both electrons located in the

sp non-bonding orbital (HOMO), and the p orbital (LUMO) empty.⁷ The singlet state is lower in energy than the triplet **2** by 48 kcal/mol,⁸ and can react in a single concerted step. Alkylidene carbenes react as either the free carbene **1** or metal carbenoid **3** depending on the generation method employed. Both forms generally give rise to the same product outcome.

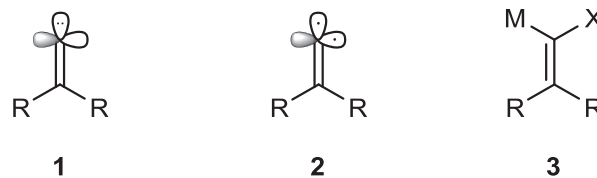


Fig. 1.

Calculations performed by Van Nhlen and Postel on alkylidene carbene **4** showed that the HOMO is delocalized over several atoms, but most of the contribution comes from the carbenic carbon (Fig. 2).⁹ The LUMO is also mainly located on the carbenic centre. NBO analysis showed that the carbene is approximately sp^{1.5} hybridized.⁹ The lone pair is predominantly s in character with 36.5% p mixing.

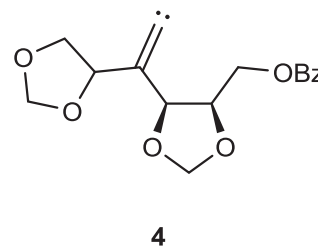


Fig. 2.

Retention of absolute configuration in 1,5 C–H insertion reactions of alkylidene carbenes suggests a mechanistic pathway without any long-lived intermediates, such as diradicals or zwitterions, which could result in the loss of stereochemical information.¹⁰ Gilbert proposed that an interaction between the empty p orbital of the carbenic carbon and the σ electrons in the C–H bond leads to a transition state such as **5**, before the insertion is complete (Fig. 3).

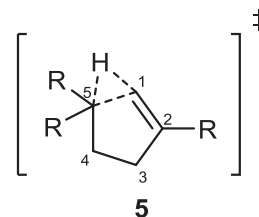
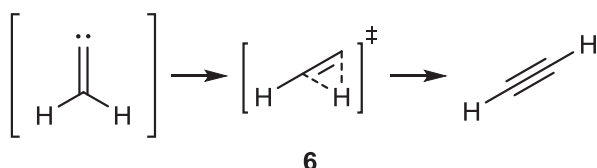


Fig. 3.

Subsequent calculations by Van Nhlen and Postel on the 1,5 C–H insertion reaction of carbene **4** are in agreement with Gilbert's original hypothesis.⁹ They reported a half chair-like transition state, with the hydrogen atom, C1, C2 and C5 all occupying the same plane. In this conformation, the C–H σ orbital and the carbene's

empty p orbital are periplanar, allowing the orbitals to overlap.⁷ This is in contrast to kinetic experiments performed by Gilbert, which suggested a non-linear transition state, with the breaking C–H bond out of the plane of C1, C2 and C5.¹⁰ While acknowledging that a non-linear arrangement would minimize any steric repulsion between the hydrogen and the carbons, Van Nhlen and Postel suggested that the long C5–H and C1–C5 distances (1.440 Å and 2.245 Å, respectively), coupled with the nearly fully-formed C1–H bond (1.168 Å), ensure minimal van der Waals repulsive interactions. They also commented that these distances suggest that the new C–H bond forms much faster than the new C–C bond, rendering the insertion process concerted, yet strongly asynchronous.⁹

A number of computational studies have been carried out on the isomerization between vinylidene and acetylene (Scheme 2).¹¹ These suggest that the 1,2-hydride migration proceeds through a transition state such as **6**, with a near-linear relationship between the two carbons and the non-migrating hydrogen atom.



Scheme 2.

While metal carbenoids **3** generally exhibit the same reactivity as the free carbenes, they differ structurally from the linear nature of **1**. The Li–Cl carbenoid **7** has been isolated and analyzed by X-ray crystallography at low temperatures by Boche et al. (Fig. 4).¹² The bond angles at C1 within the carbenoid structure are very different from those expected for an sp²-hybridized carbon. The Cl1–C1–C2 angle is 112.6(5)°, smaller than the expected trigonal angle of 120°, while the Li1–C1–C2 angle of 137.1(6)° is much larger than expected. Another feature was the elongation of the C1–Cl1 bond, which at 185.5(7) pm is longer than the mean C_{sp²}–Cl length of 172.9 pm.¹³ This elongation is in accordance with the conclusions made from analysis of ¹³C NMR spectra of simple Li-halogen alkyl carbenoids.¹⁴ Boche et al. demonstrated that similar structural features were also present in magnesium-halogen alkylidene carbenoids.¹⁵

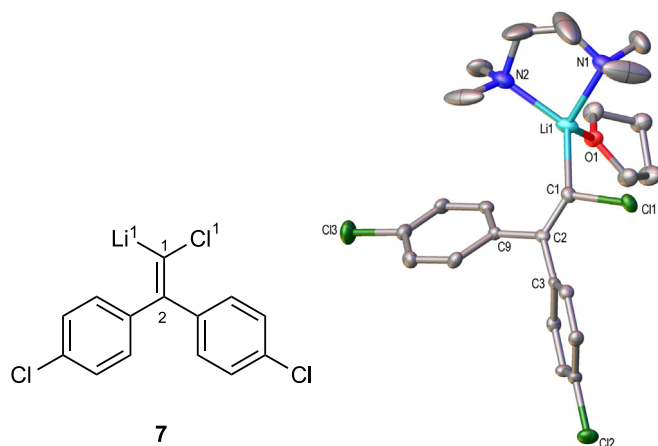


Fig. 4. Crystal structure of **7**·TMEDA·2THF with ellipsoids drawn at the 30% probability level. For clarity the second THF molecule, which is situated on a free lattice position and is not bound to the Li1 atom, has been removed. Any atoms not labelled are carbon. Data taken from Ref. 12, CSD-400037.

Table 1

Selected parameters and examples of the model CH₂=CMX at the B3LYP/6-311++G(d,p) level

	X	M	C–X (Å)	C–M (Å)	C=C–X (°)	C=C–M (°)
8a	Cl	MgCl·2(OMe ₂)	1.860	2.136	113.2	129.4
8b	Cl	H	1.751	1.082	123.4	124.4
8c	H	MgCl·2(OMe ₂)	1.101	2.122	112.2	124.1
8d	NMe ₂	MgCl·2(OMe ₂)	1.408	2.140	120.9	117.4
8e	NMe ₂	H	1.384	1.087	127.9	119.2
8f	Cl	Li·3(OMe ₂)	1.951	2.071	109.5	150.8

Kimura and Satoh have carried out DFT calculations of organo-metallic halides of general structure **8** (Fig. 5, Table 1).¹⁶

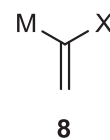


Fig. 5.

Vinylmagnesium chlorides bearing α-halo substituents, such as **8a**, were found to have substantial vinylidene character (i.e., close to sp hybridization). The carbon–halogen bond lengths were calculated to be longer than in the corresponding vinyl halides **8b**, while the C=C–X bond angles were also smaller than those of the vinyl halides. In addition, the C=C–Mg angles in α-halo vinylmagnesium chlorides were all larger than the corresponding angle in vinylmagnesium chloride **8c**.

Conversely, the C–X bond length of the vinylmagnesium chloride bearing an α-amino substituent **8d**, was shown to be similar to that of the corresponding enamine **8e**, while the C=C–Mg bond angle is smaller than vinylmagnesium chloride. The values for examples bearing α-thio and α-seleno substituents showed similar properties. This suggests that these carbenoids have little or no vinylidene character.

NBO analysis demonstrated that in vinylmagnesium chlorides bearing α-halo substituents, the carbon atom of the C–X bond had higher p-character than the corresponding vinyl halides. As such, these carbon atoms were also calculated to have higher s-character in the C–Mg bond compared to vinylmagnesium chloride.

Replacing the magnesium atom with a lithium atom **8f** resulted in an increase in vinylidene character, with the C–Cl bond longer than in both the vinyl chloride **8b** and its magnesium carbenoid derivative **8a**. In addition, the C=C–Cl bond angle was smaller and the C=C–Li bond angle larger than the corresponding vinyl chloride and vinyl-lithium, respectively. The differences in bond angles were also more marked than in the magnesium carbenoid examples.

Kimura and Satoh's calculations are in accordance with the reactivity of these substrates. α-Halo- and α-alkoxy-substituted metal carbenoids, which were calculated to have similar geometrical features, display alkylidene carbene reactivity, while those bearing α-amino and α-thio substitution react as carbanions.^{3,5,17} In addition, lithium carbenoids are known to be more reactive than their magnesium counterparts.^{3,5,17b,c,18}

Kimura and Satoh proposed that electron delocalization from the C–Mg bond into the C–X antibonding orbital was the key orbital interaction in determining the vinylidene character of α-heteroatom-substituted vinylmagnesium chlorides. The stabilization energy of the σ_{C–Mg} → σ*_{C–X} delocalization was found to be much larger for α-halo substituents than for other α-heteroatoms, suggesting that the carbanion is stabilized by this interaction. This interaction is also responsible for the lengthening of the C–X bond.

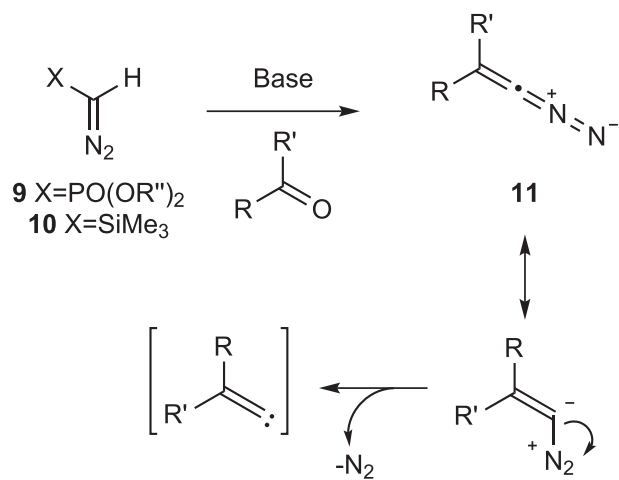
3. Methods of generation

The high reactivity of alkylidene carbenes necessitates their *in situ* generation. The techniques commonly utilized employ the use of diazo olefination reagents, haloalkenes and alkynylidonium salts. In all cases, the reactive species is generally represented as the free alkylidene carbene, although it is not clear to what extent reactions proceed through this high-energy intermediate. However, where comparisons are possible, the same product outcome is generally observed.

3.1. Nitrogen extrusion

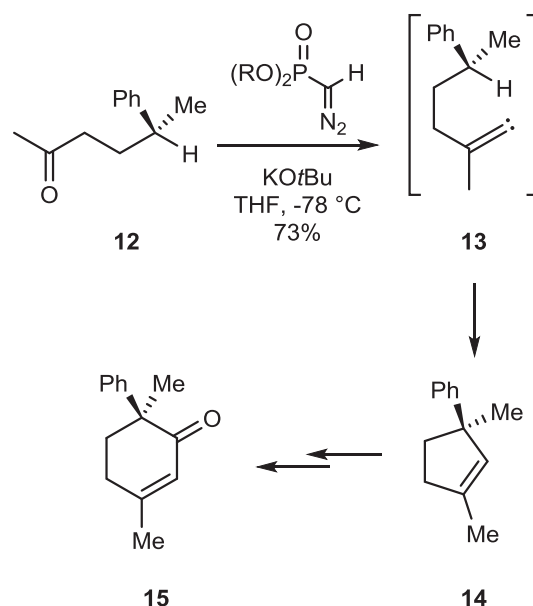
One of the most widely employed methods by which to access alkylidene carbenes is the loss of N₂ from a double bond terminus, in particular from 1-diazoalkenes. The simplest, and most commonly used, technique for accessing diazoalkenes is the reaction of aldehydes or ketones in a modified Horner–Wadsworth–Emmons reaction,¹⁹ or in a modified Peterson olefination.²⁰ These reactions employ the use of diazomethylphosphonate (DAMP) esters **9** (Seyferth–Gilbert reagent) and trimethylsilyldiazomethane (**10**), respectively. While trimethylsilyldiazomethane is commercially available, it is necessary to synthesize the phosphonate esters.

The reaction proceeds through the established mechanism for both the Horner–Wadsworth–Emmons and Peterson reactions, with initial nucleophilic attack on the carbonyl functionality by the deprotonated olefination reagent, with subsequent elimination to give the 1-diazoalkene **11**. Unlike α -diazo carbonyls, which often requires a metal catalyst to facilitate the extrusion of nitrogen at a reasonable temperature,^{1d} 1-diazoalkenes readily undergo the loss of nitrogen to produce alkylidene carbenes (Scheme 3).



Scheme 3.

The intramolecular C–H insertion reaction of alkylidene carbenes proceeds with remarkable selectivity, producing five-membered rings, irrespective of the substitution pattern present, and generating secondary, tertiary and quaternary centres. Additionally, the stereospecificity of the reaction results in retention of absolute configuration at a stereogenic centre.²¹ An early example of the remarkable stereospecificity of the 1,5 C–H insertion reaction of alkylidene carbenes was the synthesis of cyclopentene **14** from the enantiopure ketone **12** by Gilbert in 1985, via alkylidene carbene **13** (Scheme 4).¹⁰ Upon conversion to enone **15**, the insertion reaction was found to proceed with a stereoselectivity of at least 99%. This retention of absolute configuration is strong evidence that the alkylidene carbene is reacting through the singlet state.



Scheme 4.

Wardrop reported the formation of dihydrofurans **18** and **19** through treatment of the α and β isomers of ketone **16** with lithiated trimethylsilyldiazomethane **17** (Scheme 5).²² This example demonstrates the retention of absolute configuration associated with 1,5 C–H insertion adjacent to heteroatoms.

Diazo olefination reagents have also been used extensively in the synthesis of terminal alkynes from aldehydes,^{6,23} and diaryl alkynes from ketones.²⁴

The use of the modified Peterson conditions has been extended to the synthesis of 2,3-dihydrofurans **21** and **23** from ketones **20** and **22**, via formal 1,5 O–H and O–Si insertions, respectively.²⁵ This appears to be the only case of a direct comparison between O–H and O–Si insertion, and suggests that O–Si insertion is more efficient (Scheme 6).

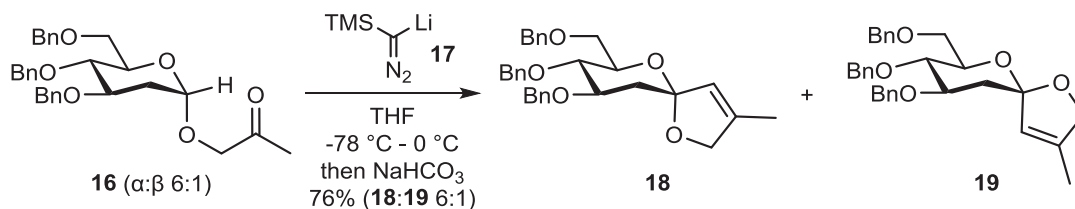
It is believed that these products form through one of two possible mechanisms (Scheme 7).²⁶ The alkylidene carbene **24** can undergo insertion into the O–Si bond, forming dihydrofuran **25** directly via a transition state similar to that for C–H insertion. Alternatively, the reaction could proceed through the formation of an oxonium ylide **26**, followed by a 1,2-shift (Stevens rearrangement) of the oxygen substituent.

Similar pathways involving intramolecular insertion into N–H bonds or interactions with nitrogen lone pairs to form 2-pyrrolines have also been reported.²⁷

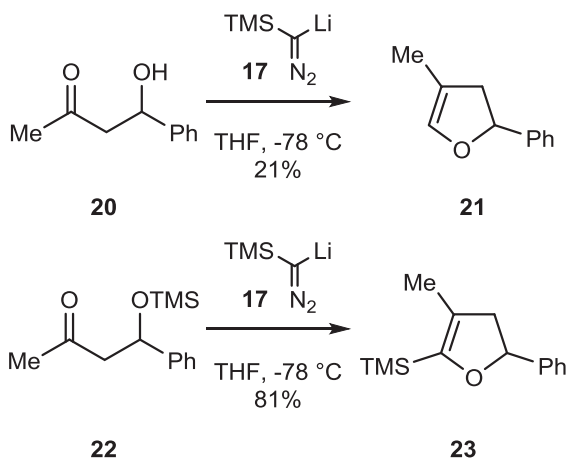
Diazo olefination reagents have been utilized in the discovery of new alkylidene carbene reaction pathways. Daesung Lee reported the synthesis of silylated cyclopropenes through the generation of alkylidene carbenes from α -silyl ketones using Peterson-type reaction conditions.²⁸ Treatment of citronellal **27** with trimethylsilyldiazomethane in the presence of catalytic InCl₃ allowed access to α -silyl ketone **28**. This was subsequently treated, without purification, with lithiated trimethylsilyldiazomethane **17**, giving rise to cyclopropene **29** in 77% yield (Scheme 8). Cyclopentene **30**, the expected product of 1,5 C–H insertion, was not observed.

D. Lee proposed that the cyclopropene arose from the insertion of the alkylidene carbene into the nearby C–Si bond, suggesting that the interaction between the empty p-orbital of the carbene and the C–Si σ -bond was more favourable than the interaction with the more remote C–H σ -bond (Scheme 9).

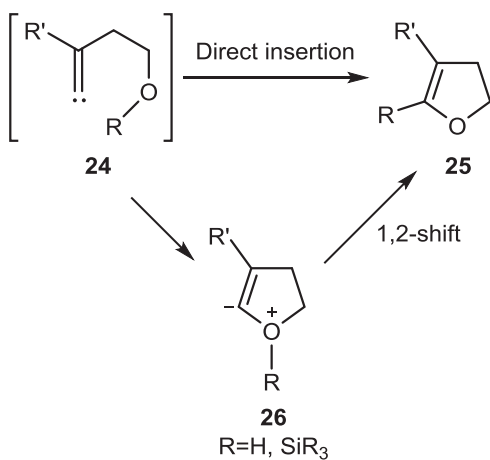
The reaction was performed on a range of substrates, including those containing straight- and branched-chain alkyl groups,



Scheme 5.



Scheme 6.



Scheme 7.

varying degrees of unsaturation (both *cis* and *trans*) and aromatic substituents. Five-membered ring formation was only observed in cases where 1,5 C–H insertion was promoted by an adjacent oxygen atom (*vide infra*) (Scheme 10). Even so, cyclopropanes remained the major products isolated, suggesting that the 1,3 C–Si insertion pathway is much more favourable.

Alkylidene carbenes can undergo [2+1] cycloaddition reaction with alkenes, giving rise to bicyclo[3.1.0]hex-1-ene derivatives. For example, alkylidene carbene **33**, generated by the reaction of ketone **31** with **17**, underwent intramolecular [2+1] cycloaddition reaction with the tethered alkene, giving rise to the bicyclo[3.1.0]hex-1-ene **34**.²⁹ In situ fragmentation of this strained ring system generated trimethylenemethane diyl **35**,³⁰ which afforded linearly fused triquinane **32** through a stereoselective intramolecular [3+2] cycloaddition reaction (Scheme 11).^{30b} Hee-Yoon Lee has expanded his work in this area to generate the initial alkylidene carbene from

both α,β -epoxy-*N*-aziridinylimines^{30a} and alkynylidonium salts.^{30c,d}

Bicyclo[3.1.0]hex-1-ene systems generated from alkylidene carbenes can also dimerize via an intermolecular [2+2] cycloaddition reaction to give polycyclic systems.³¹

Alkylidene carbenes can also undergo [2+1] cycloaddition reaction with the π -system of aromatic rings.³² Shioiri reported the synthesis of cyclohepta[*b*]pyrrol-2-ones **37** from the reaction of α -keto anilides **36** with **17** (Scheme 12).^{32a} Insertion of the alkylidene carbene **38** into the aromatic π -system affords norcaradiene **39**, which rearranges to the product cycloheptatriene **37**. Interestingly, reaction with the π -system occurs in preference to 1,5 C–H insertion into the *N*-methyl group, as the corresponding *N*-aryl pyrrol-2-ones were only observed as byproducts in some cases.

While modified olefination reagents are undoubtedly useful for the *in situ* generation of alkylidene carbenes, a potential drawback is the strongly basic conditions required for their use. The thermal decomposition of α,β -epoxy-*N*-aziridinylimines **40** allows for the generation of alkylidene carbenes under neutral conditions.³³ This approach also offers an additional benefit, allowing for the generation of an alkylidene carbene with a β -hydroxyl group. The decomposition is thought to proceed in a similar fashion to the Eschenmoser fragmentation.³⁴ Heating **40** in toluene generates diazo compound **41**, with concurrent loss of styrene. Opening of the epoxide generates the double bond, and proton transfer from the vinyl carbon to the oxygen in betaine **42** leads to diazonium ylide **43**, which extrudes nitrogen, resulting in β -hydroxy alkylidene carbene **44** (Scheme 13). The *N*-aziridinylimines are readily available by treating the corresponding carbonyl compound with *N*-aziridinylamines.

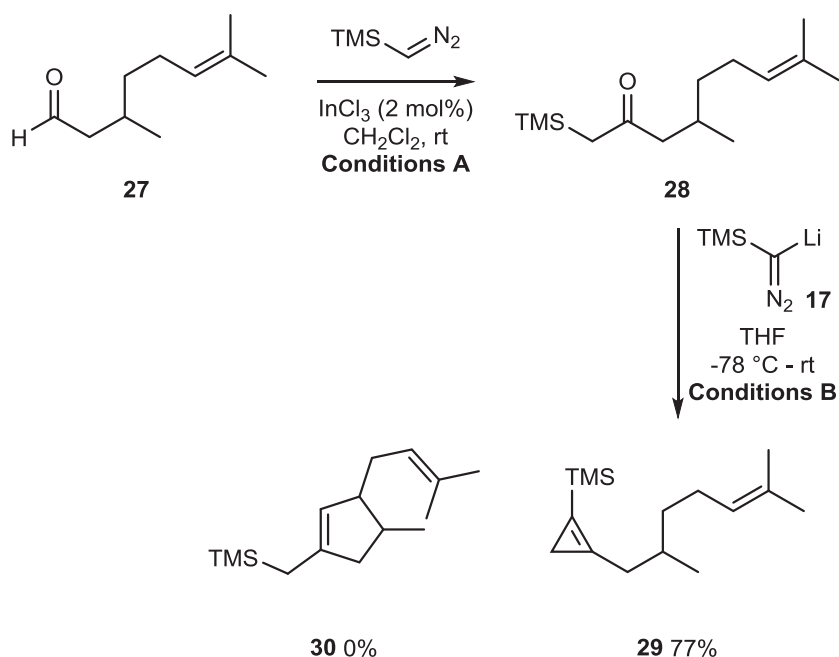
Kim utilized this methodology to synthesize propargyl alcohols and cyclopentenols,^{26a} and later expanded the scope of this reaction to include the formation of silylated dihydrofurans through a formal 1,5 O–Si insertion (Scheme 14).³⁵

Four-membered heterocycles open under similar conditions.³⁶ Thus, α -oxetanyl-*N*-aziridinylimines gave dihydrofurans via 1,5 O–H insertion, while α -azetidyl-*N*-aziridinylimines gave homopropargyl amines via 1,2-migration (Scheme 15). When heterocyclic systems larger than four-membered rings were employed, then the reaction pathway did not proceed through the alkylidene carbene, suggesting that the relief of ring strain plays a key role in the generation of this reactive intermediate.

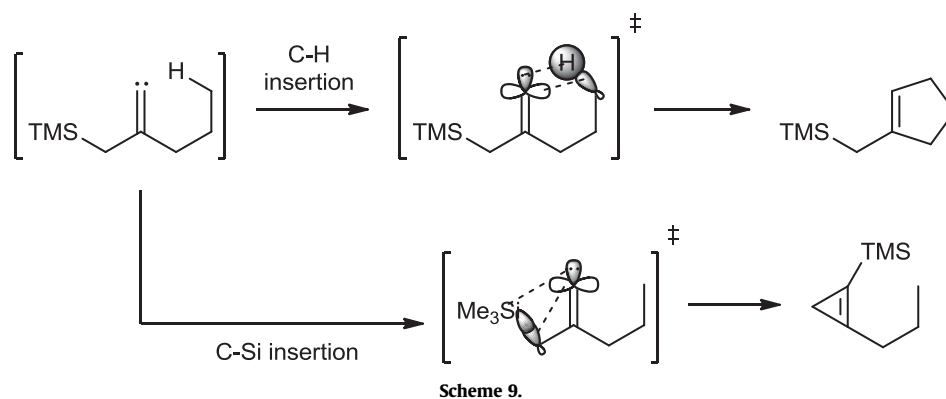
Related to the loss of nitrogen from 1-diazoalkenes is the fragmentation of tetraazafulvenes **45** to give alkylidene carbenes, with the concurrent loss of two molecules of nitrogen (Scheme 16). Like diazoalkenes, tetraazafulvenes are unstable and it is necessary to generate them *in situ* from more stable precursors. The use of tetrazoles to generate alkylidene carbenes was first reported by Behringer in 1966,³⁷ but further development of this chemistry has only occurred in recent years.

In 2005, Van Nhlen and Postel described the synthesis of dihydrofuran **47** when cyanomesylate **46** was treated with TMSN_3 in the presence of Bu_2SnO (Scheme 17).³⁸

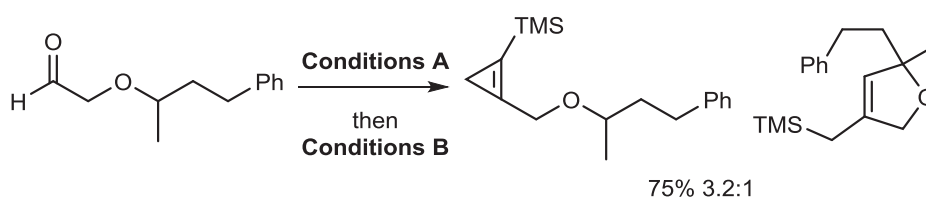
They postulated that the reaction proceeded through initial cycloaddition between the nitrile group and TMSN_3 , affording tetrazole



Scheme 8.



Scheme 9.



Scheme 10.

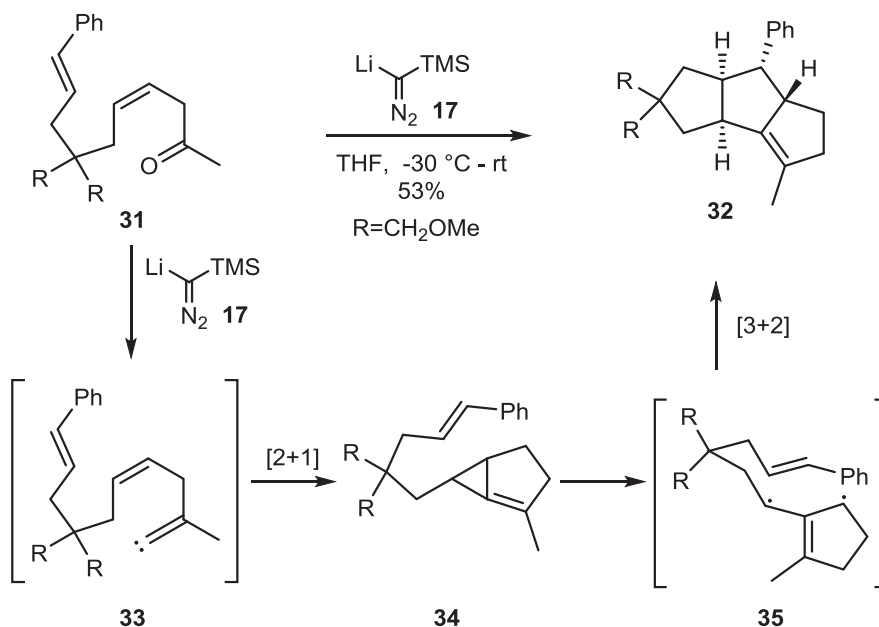
48. Desilylation and rearrangement to 1*H*-tetrazole anion **49** is followed by elimination of the mesylate to give the tetraazafulvene **45**. The extrusion of two molecules of N₂ gives the alkylidene carbene, which undergoes subsequent 1,5 O–Si insertion (Scheme 18). The Bu₂SnO is present to accelerate the initial cycloaddition.³⁹

Two less common reaction pathways of alkylidene carbenes were demonstrated using this methodology.³⁸ Intermolecular [2+1] cycloaddition of the alkylidene carbene generated from cyanomesylate **50** gave **51** as a mixture of diastereoisomers, while cyanomesylate **52** was converted to dihydropyran **53**, the product of an alkylidene carbene 1,6 C–H insertion reaction, albeit in modest yield (Scheme 19).³⁸ The product was isolated as a mixture

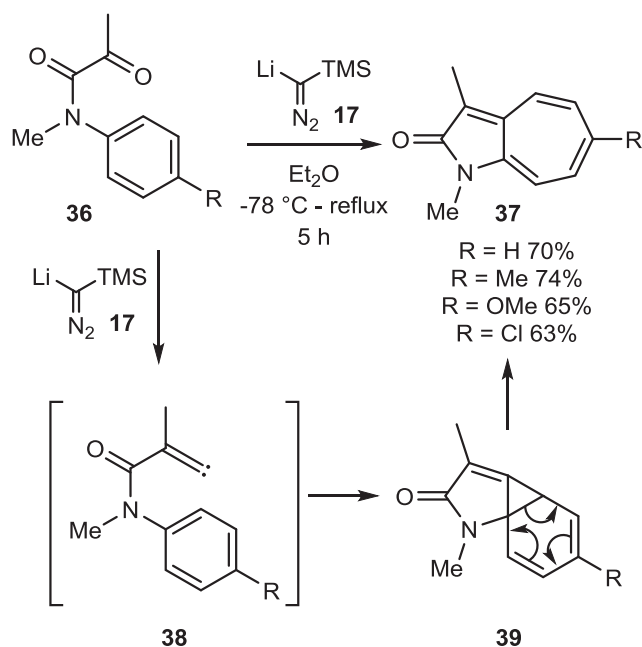
of diastereoisomers. Feldman had previously demonstrated 1,6 alkylidene carbene insertion reactions using naphthol and anthrol systems, suggesting that this reaction can occur in systems where the 1,5 insertion pathway was blocked.⁴⁰

Wardrop has also reported the generation of alkylidene carbenes via tetraazafulvenes **45**, accessing them through dehydration of 5-hydroxy-1*H*-tetrazoles **54** with carbodiimides (Scheme 20).⁴¹

The 5-hydroxyalkyl-1*H*-tetrazoles **54** were readily prepared in two steps from precursor carbonyl compounds via addition of 1-allyl-5-tetrazoyllithium **55** followed by Ni-catalyzed *N*-deallylation in the presence of ^tBuMgCl (Scheme 21). A range of substrates were prepared this way, mostly in good yields.



Scheme 11.



Scheme 12.

Treatment of 5-hydroxyalkyl-1*H*-tetrazoles with a range of carbodiimides afforded alkynes via 1,2-migration of phenyl and hydrogen groups in good yield, with diisopropylcarbodiimide (DIC) giving the best results (Scheme 22).

Unsaturated ring systems could also be synthesized in reasonable yields using this methodology through 1,5 C–H insertion reactions of the intermediate alkylidene carbenes (Scheme 23). The conditions required were more forcing than those for the 1,2-migration reaction, with refluxing DCE needed to ensure conversion.

Nitrogen extrusion from double bond termini is a versatile means for accessing alkylidene carbenes, especially as the necessary precursors are readily available from carbonyl compounds. The development of tetraazafulvene and *N*-aziridinylimines precursors enable alkylidene carbenes to be generated under neutral

conditions. In addition, *N*-aziridinylimines generate additional alcohol functionality within the target molecule.

3.2. α -Elimination of metal carbenoids

Alkylidene carbenes can be generated through the reductive elimination of metal carbenoids, also known as metal vinylidenes (Scheme 24).^{5,42} Despite being structurally different to 'naked' alkylidene carbenes, carbenoids display the same reactivity, undergoing 1,2-migration and 1,5 insertion reactions. Despite this, it is unclear to what degree the metal salt is fully dissociated from the carbene prior to reaction. Labelling studies have shown that in the 1,2-migration of diaryl alkylidene carbenoids, the aryl group trans to the halogen preferentially migrates to give the resulting alkyne.⁴³

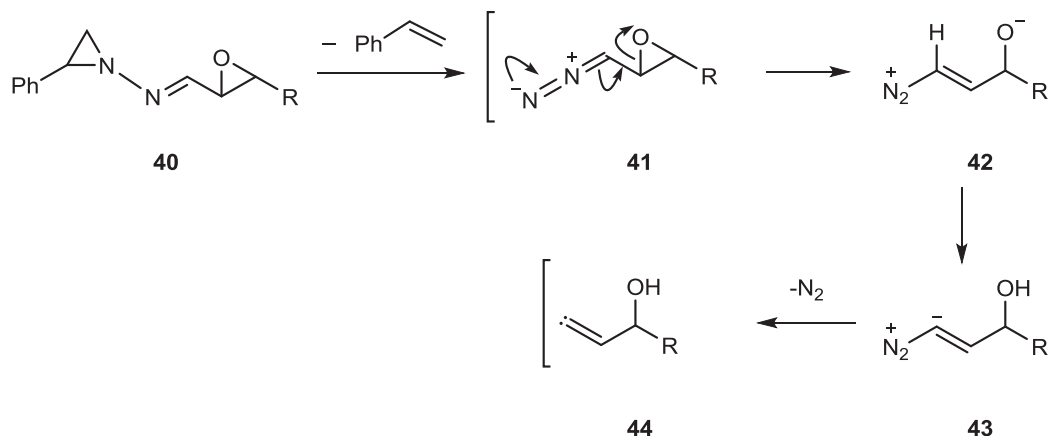
Alkylidene carbenoids are readily available through a variety of methods. One of the most widely used is through the base-induced elimination of vinyl halides⁴⁴ or vinyl triflates.^{23a,45} Ohira reported the synthesis of cyclopentene **56** from vinyl triflate **55** using KO^tBu as a base (Scheme 25).⁴⁵

The most commonly employed tactic for accessing these carbenoids is the deprotonation of vinyl halides. Taber reported the use of NaHMDS to synthesize cyclopentene **58** in good yield from vinyl chloride **57**,^{44d} while Hayes prepared 3-pyrroline **60** through treatment of vinyl bromide **59** with KHMDS, without the need to protect the secondary amine (Scheme 26).⁴⁶ In both cases retention of absolute configuration at the 1,5 C–H insertion site adjacent to the heteroatom is observed.

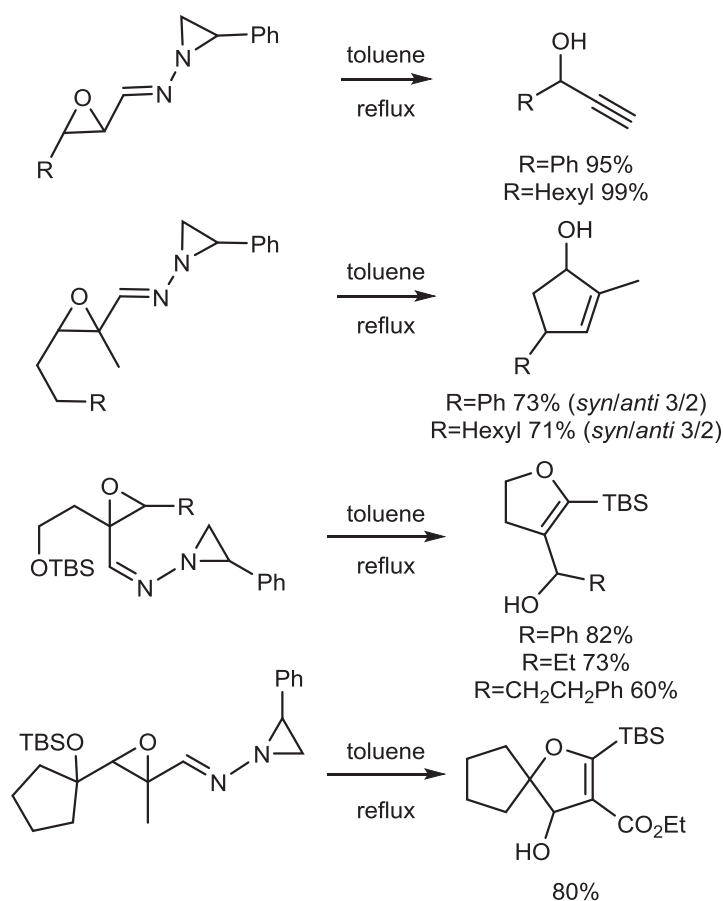
Alternatively, metal carbenoids can be accessed via metal–halogen exchange of a dihaloalkene. Tykwinski employed this strategy in the synthesis of polyynes via a 1,2-migration, including triyne **62** in good yield from dibromoalkene **61** (Scheme 27).⁴⁷ This reaction was also the first example of an alkynyl group undergoing 1,2-migration.^{47,48} This method has been widely used in the synthesis of polyynes.⁴⁹

Tani reported the formation of fused cyclopentene **64** by treating dihaloalkene **63** with excess SmI₂ and HMPA (Scheme 28).⁵⁰

While the reaction shown in Scheme 27 is believed to proceed through lithium–halogen exchange, the transformation in



Scheme 13.



Scheme 14.

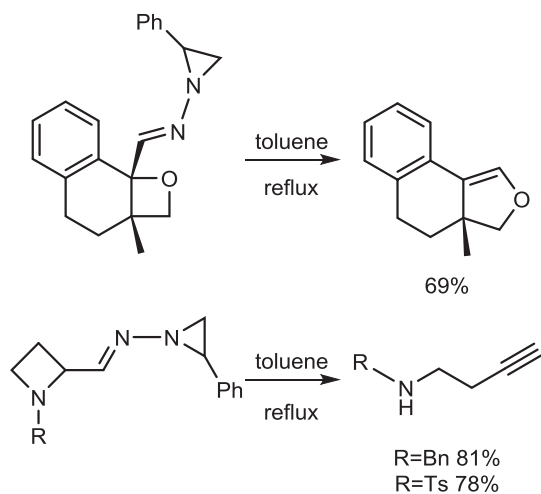
Scheme 28 is more likely to proceed via electron transfer followed by loss of the halide anion from dihaloalkene **65** to give vinyl radical **66**. Further reduction by a second equivalent of SmI_2 gives carbenoid **67**, which reacts to form the cyclopentene **68** via 1,5 C–H insertion (Scheme 29).⁵⁰

The use of vinyl halides and dihaloalkenes as precursors to alkylidene carbenes is attractive as these functionalities are readily available via carbonyl olefination.^{44d,47,51} However, other methods of accessing alkylidene carbenoids, which are not reliant on manipulation of a carbonyl functional group, have also been reported. Suzuki described the generation of zirconium

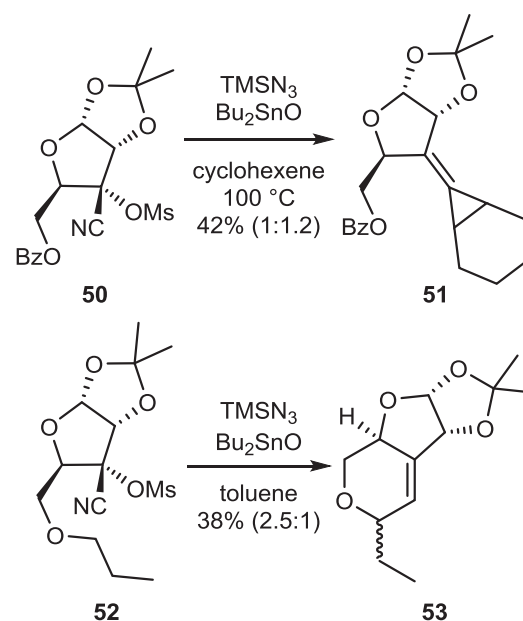
alkylidene carbenoids via allylzirconation of iodoalkynes in the presence of methylaluminoxane (MAO).⁵² The allylzirconium reagents themselves were accessed via hydrozirconation of allenes (Scheme 30).

This methodology was applied to the synthesis of a range of aryl-substituted enynes from aryl iodoalkynes (Scheme 31).

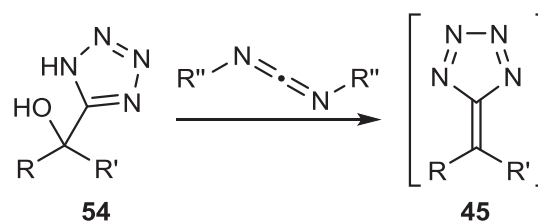
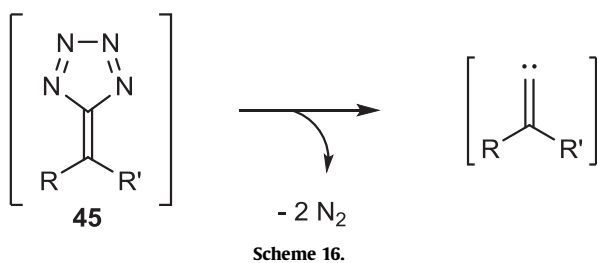
When the same methodology was applied to alkyl-substituted iodoalkynes, the products observed were again the product of 1,2-migration, even in cases where 1,5 C–H insertion was possible (Scheme 32). Higher temperatures were required for this reaction, and lower yields of the products were observed.



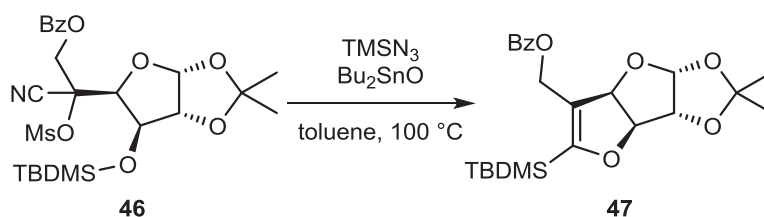
Scheme 15.



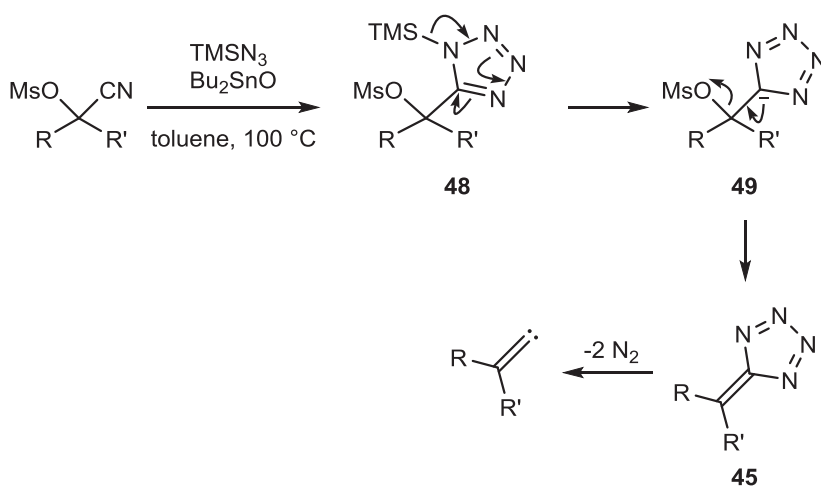
Scheme 19.



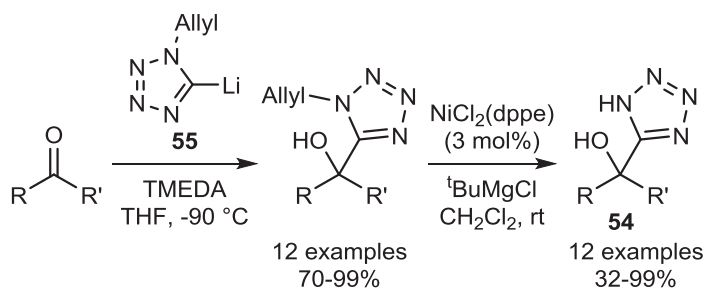
Scheme 20.



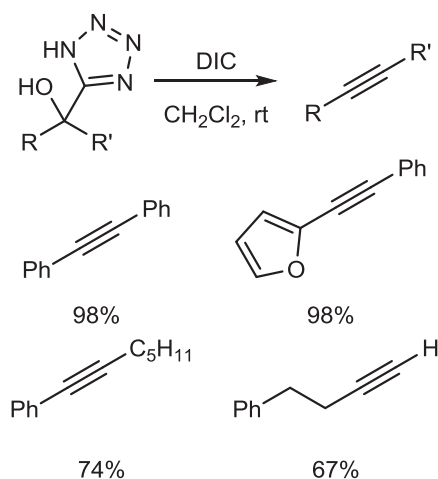
Scheme 17.



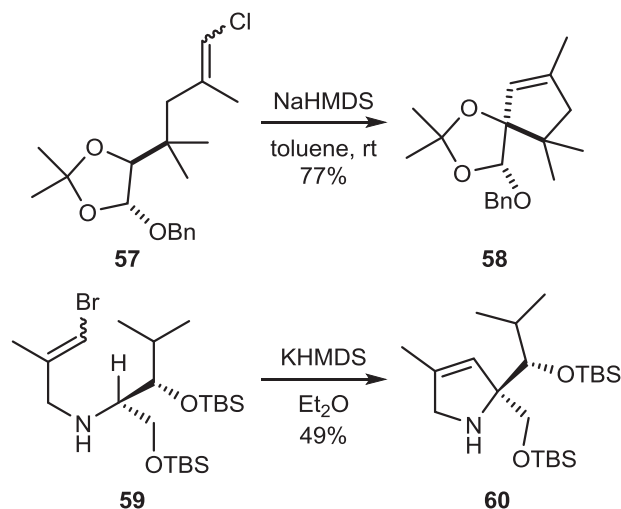
Scheme 18.



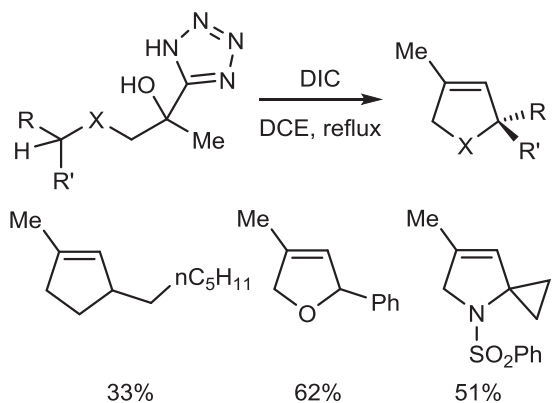
Scheme 21.



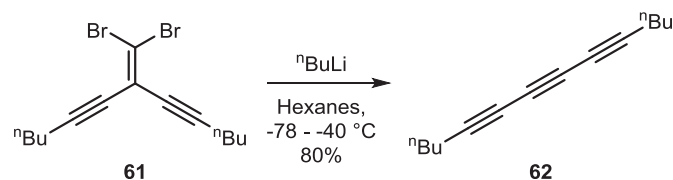
Scheme 22.



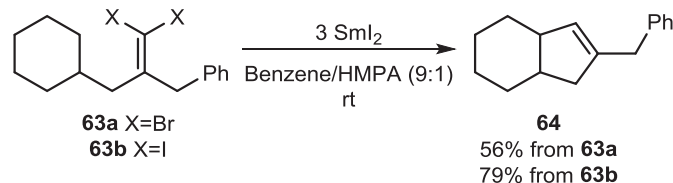
Scheme 26.



Scheme 23.



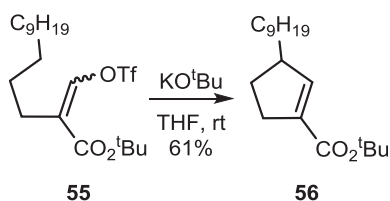
Scheme 27.



Scheme 28.



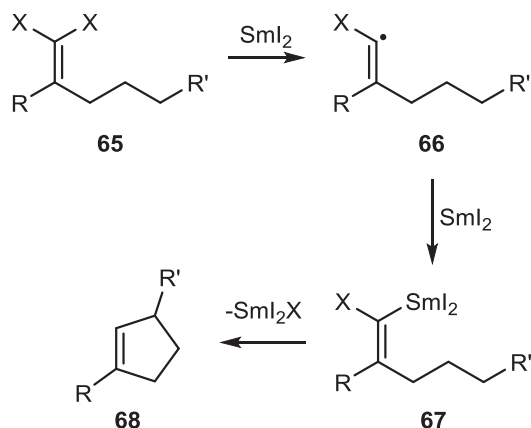
Scheme 24.



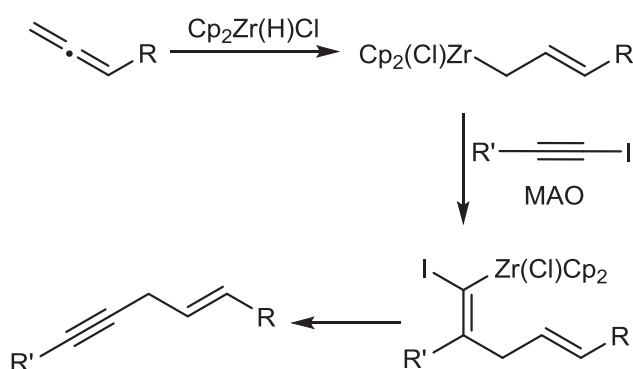
Scheme 25.

NMR labelling studies of the reaction showed a clear difference in how the two substrate classes proceeded through the reaction. When the ^{13}C -labelled iodoalkyne **69** was subjected to the reaction conditions, the product **70** had the ^{13}C label directly attached to the naphthyl group, consistent with a 1,2-shift of the aryl group. However, in the reaction with the labelled alkyl iodoalkyne **71**, the product **72** showed no change in the position of the ^{13}C label, suggesting that, in this case, the migrating group was the allyl substituent (Scheme 33).

These results suggest that, in the absence of more suitable migratory groups, the allyl functionality is able to undergo a 1,2-migration reaction, giving rise to alkynes. The lack of evidence of



Scheme 29.



Scheme 30.

any 1,5 C–H insertion products suggests that this process is faster than any competing insertion pathways.

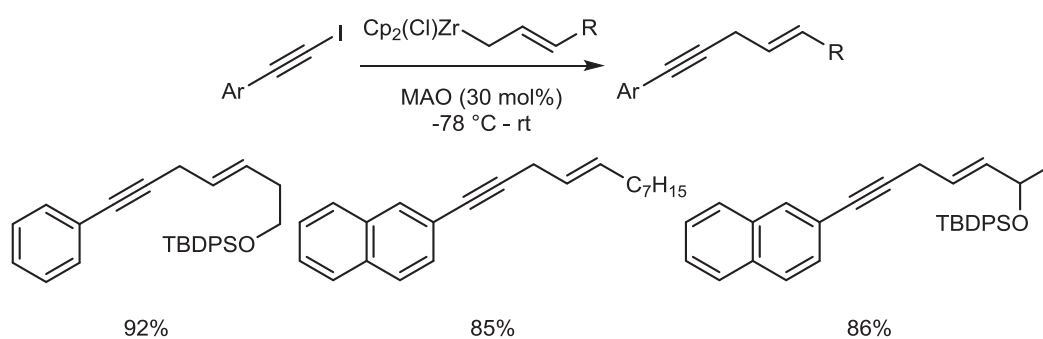
Normant has described the synthesis of alkynes from zinc carbenoids, generated from bismetallalkenes.⁵³ Treatment of alkylnyllithium **73** with allyl Grignard gave rise to bismetallalkene **74**, which reacts stereoselectively with phenylsulfonyl chloride to give alkylidene carbenoid **75**.⁵⁴ At low temperatures, **75** can be quenched with a second halogenating reagent. However, if the reaction is warmed to room temperature, **75** cleanly rearranges to give the alkyne **76** (Scheme 34).

Normant was able to demonstrate the stereospecificity of the migration. By quenching the bismetallalkene **78** with acid, it could be seen that the initial addition of the allyl Grignard to the alkylnyllithium **77** occurred with a diastereomeric ratio of 92:8. Since **80** is also formed as a 92:8 mixture of diastereoisomers, the generation of alkylidene carbenoid **79** and its subsequent rearrangement to alkyne **80** occurs in a stereospecific fashion (Scheme 35).

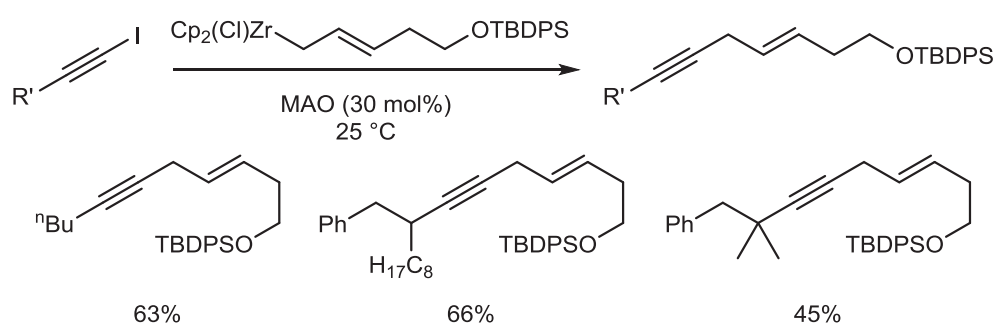
To determine whether the migration had occurred with retention or inversion, **80** was fully reduced and the MEM group removed to give **81**. By comparing the sample of **81** synthesized in this manner to a sample of known stereochemistry, it was shown to be the *syn* isomer. Thus, it was concluded that the migration occurred with complete retention of absolute configuration.

NMR studies were again employed to determine which group underwent migration.^{53b} Generation of ¹³C-labelled carbenoid **82** gave rise to enyne **83**, indicating that the ether carbon trans to the chlorine was migrating in this case (Scheme 36).

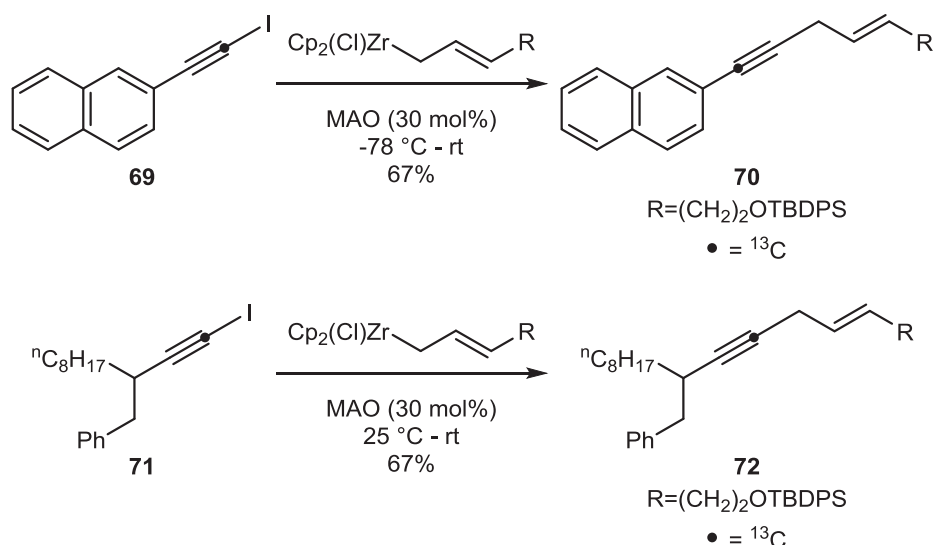
The absence of the chelating substituent drastically reduced the stereoselectivity of the carbenoid formation, as was seen by the low *E/Z* ratios of vinyl chlorides **86a–c** formed when carbenoid **85** was quenched with acid (Scheme 37). However, this appears to have had little or no bearing on the outcome of the reaction, as the formation of enynes occurred with higher selectivity. The reaction of **84a** gave **87a** and **87b** in a ratio of 92:8 indicating that the allyl group preferentially migrates, regardless of whether it is *cis* or *trans*



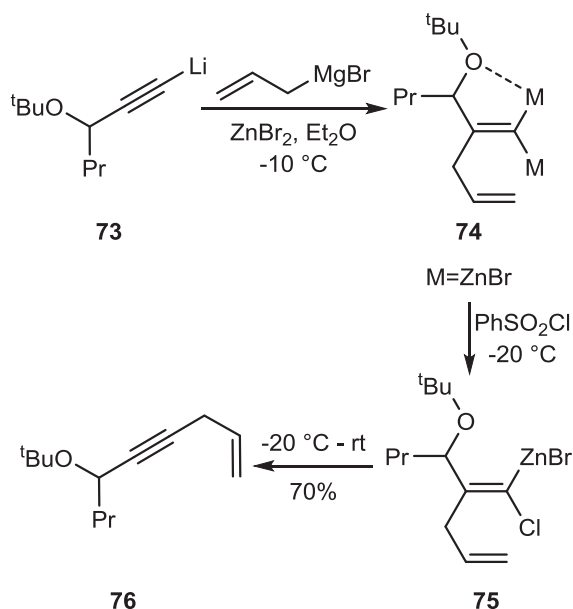
Scheme 31.



Scheme 32.



Scheme 33.



Scheme 34.

of products, with the desired alkyne isolated in less than 10% yield.^{53a}

Alkylidene carbenoids have also been generated via the intramolecular cyclization of alkynyllithiums.⁵⁶ Harada reported a tandem cyclization process upon treating alkynes with base (Scheme 38).^{56b} While the reactions were largely carried out with iodides, this transformation could also be performed on sulfonates. NaHMDs or KHMDS served as alternative bases to LDA.

Harada proposed that the reaction proceeded via 5-*exo-tet* cyclization of the nucleophilic alkynyllithium, generating the alkylidene carbenoid **90**. This subsequently underwent C–H insertion, forming the second ring with high diastereoselectivity (Scheme 39). This route stands in contrast to the synthesis of similar systems using alkynylidonium species, where the alkyne serves as an electrophile (vide infra).^{32b,57}

3.3. Metal vinylidenes

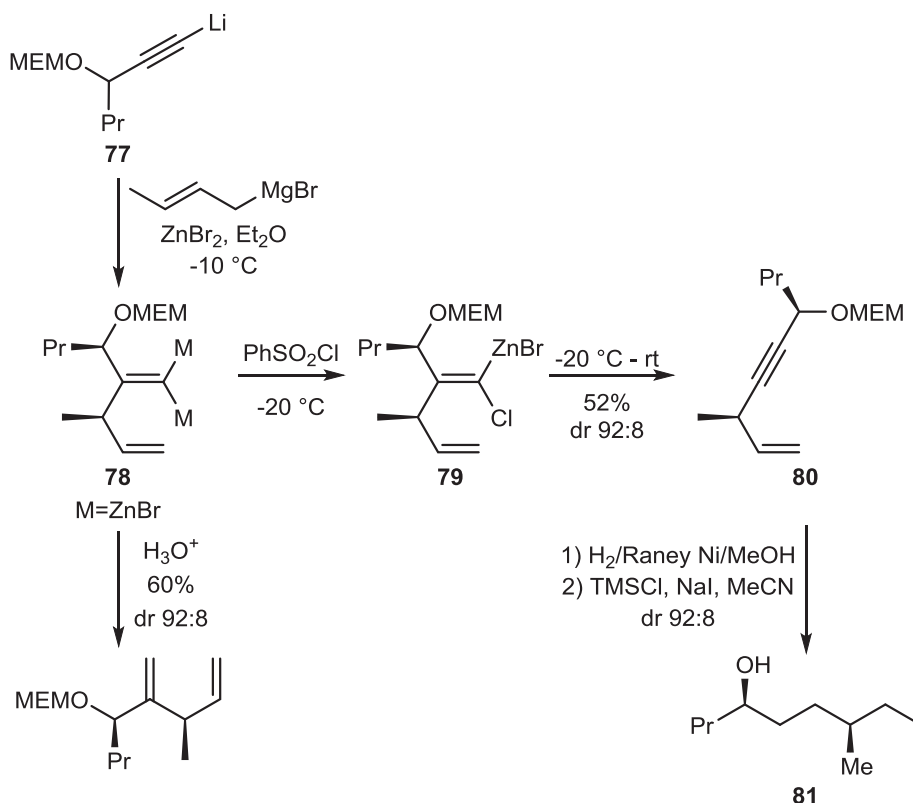
Catalytic methods for accessing alkylidene carbenoids have also been developed, with metal vinylidene complexes being proposed as intermediates in several carbon–heteroatom and carbon–carbon bond forming processes.⁵⁸ Yamamoto reported the conversion of aryl-substituted terminal alkynes into functionalized indenenes using catalytic PtBr_2 (Scheme 40).⁵⁹ Yamamoto proposed that the reaction proceeded via isomerization of the alkyne to the Pt-vinylidene complex, which underwent 1,5 C–H insertion to give the product. Liu⁶⁰ and Chatani⁶¹ have reported similar reactions using platinum and ruthenium catalysts, but suggested that the vinylidene intermediate didn't undergo direct C–H insertion, instead proceeding through a 1,5 hydride shift followed by a cycloisomerization. In 2015, González utilized iodoalkynes in a similar reaction, using a gold catalyst to synthesize 3-iodoindenenes via 1,5 C–H insertion.⁶²

Zhang and Hashmi independently reported the dual activation of aromatic diynes,⁶³ using a gold catalyst to access the intermediate gold vinylidene via a carbocyclisation route similar to that described by Harada.⁵⁶ Zhang reported the synthesis of a range of fused polycycles from diynes employing a strategy, which utilized the activation of both alkynes (Scheme 41).^{63e}

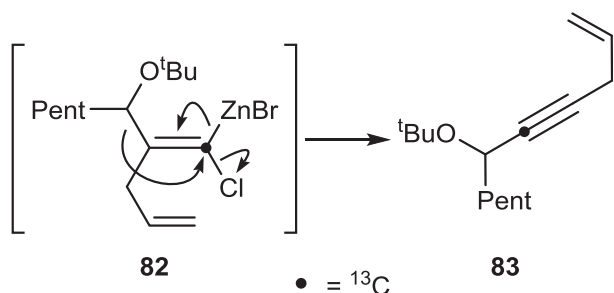
Zhang proposed that the reaction proceeds through the formation of alkynylgold complex **91**, with the *N*-oxide acting as a base to remove the proton from the terminal alkyne. The internal alkyne

to the chloride leaving group. Similarly, the observation that **88a** is the major product in the reaction of **84b** indicates preferential migration of the substituted allyl group over the cyclohexyl, albeit less so than the allyl group itself. Additionally, the predominance of **89b** shows that the octyl group migrates in preference to the substituted allyl, even if it is primarily *cis* to the chlorine.

The extensive work on zirconium and zinc carbenoids, by Suzuki and Normant, respectively, has demonstrated that under the right conditions, alkyl-substituted alkylidene carbenoids undergo 1,2-migration reactions to form alkynes. It is also important to note that no evidence of 1,5 C–H insertion was reported, despite this generally being the preferred pathway for alkylidene carbenes bearing alkyl groups. While there have been several reports of differing reactivity of alkylidene carbenoids and 'free' carbenes (vide infra),⁵⁵ these results suggest that altering the coordinating metal may also affect the reactivity. Normant reported that the corresponding lithium carbenoid gave a complex mixture



Scheme 35.



Scheme 36.

is then activated by another molecule of the catalyst, giving **92**, which undergoes a 5-*endo-dig* cyclization, resulting in the formation of gold vinylidene **93**. A 1,5 C–H insertion reaction of **93** leads to **94**, which gives the product after protodeauration (Scheme 42). This mechanism was supported by computational studies.^{63e} Propargylic alcohols and amines undergo analogous O–H and N–H insertions, leading to furans and pyrroles.

Hashmi reported the synthesis of similar polycyclic systems from aromatic diynes, again employing a double activation strategy under gold catalysis.^{63a–d,f} Van der Eycken utilized this methodology to synthesize cyclopentapyridinones,⁶⁴ while Ohno reported the synthesis of bi- and tricyclic pyrroles from *N*-propargyl ynarnides under similar conditions.⁶⁵ Hashmi also reported the synthesis of benzothiophenes and benzofurans using similar chemistry, albeit via a different mechanism.⁶⁶ The need for dual activation can be avoided by generating gold alkylidene carbenoids via cyclization onto alkyl sulfonates.⁶⁷

Metal vinylidenes such as those described above also undergo reaction with external nucleophiles. Osmium, platinum and ruthenium vinylidenes have been shown to react with H₂O to form

hydroxy carbenes, which then tautomerize to the metal acyl species.⁶⁸ These can then undergo elimination to the aldehyde, or extrude CO to form the reduced organic compound and the corresponding metal carbonyl (Scheme 43). Fukumoto reported the synthesis of nitriles via reaction of the intermediate ruthenium vinylidene with *N,N*-dimethylhydrazine.⁶⁹

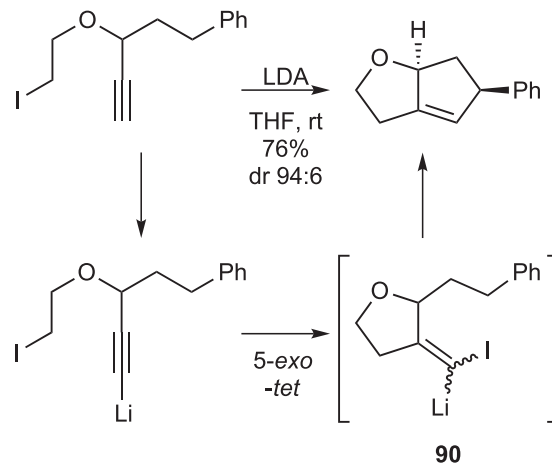
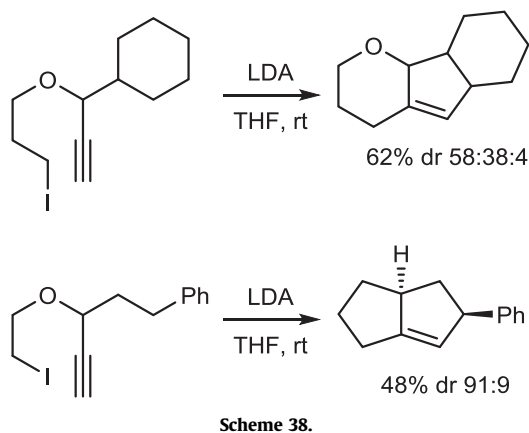
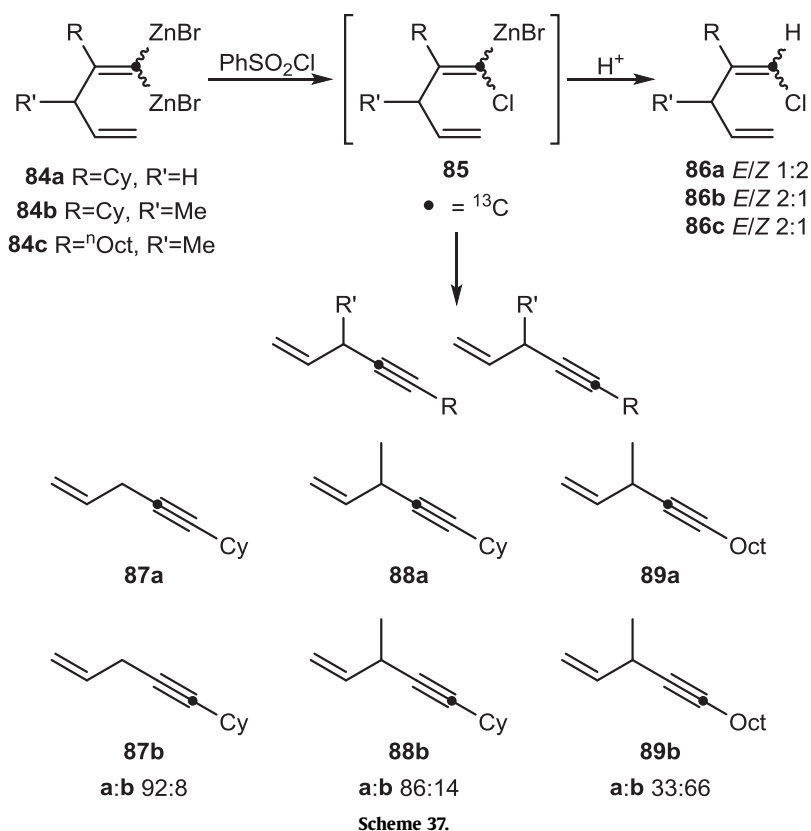
In 2015, Hashmi combined this reactivity with the dual gold activation of diynes to synthesize functionalised indenenes in good yields (Scheme 44).⁷⁰

The use of metal carbenoids offer a viable alternative to access alkylidene carbenes, particularly since many can be accessed from the same carbonyl precursors as diazo olefination reagents. The research by Normant and Suzuki into zinc and zirconium carbenoids, respectively, has not only expanded the techniques by which alkylidene carbenoids can be generated, but has also increased the understanding of the reactivity of these useful intermediates. The formation of metal vinylidenes under catalytic conditions is a significant breakthrough as previous reactions involving alkylidene carbenes required stoichiometric generation of the reactive intermediates.

3.4. Hypervalent iodine

The use of hypervalent alkynyl iodides is a complementary method for alkylidene carbene generation.^{4a,b,d} In contrast to the methods above, which typically rely on carbonyl precursors, the use of hypervalent halides allows access to heteroatom-substituted alkylidene carbenes.

Alkylidene carbenes are generated via the reductive elimination of iodonium ylides. Similar to the deprotonation of vinyl halides, treating hypervalent vinyl iodonium salts with base leads to an iodonium ylide. Ochiai utilized this approach in the synthesis of alkynyl sulfides and sulfoxides.⁷¹ This process demonstrated the



tendency for sulfenyl and sulfinyl substituted alkylidene carbenes to undergo 1,2-migration (Scheme 45).

A much more common approach to hypervalent vinyl iodonium ylides is the addition of nucleophiles to alkynylaryliodonium salts, also referred to as 1-alkynyl(aryl)- λ^3 -iodanes.^{4a,b,d} Aryliodine(III) groups are strongly electron-withdrawing⁷² as well as demonstrating considerable leaving group ability,⁷³ making them ideal for this kind of transformation. The initial Michael addition to the iodonium species results in an iodonium ylide, which reductively eliminates the aryl iodide to give the corresponding carbene, with the initial nucleophile being incorporated into the final product (Scheme 46).

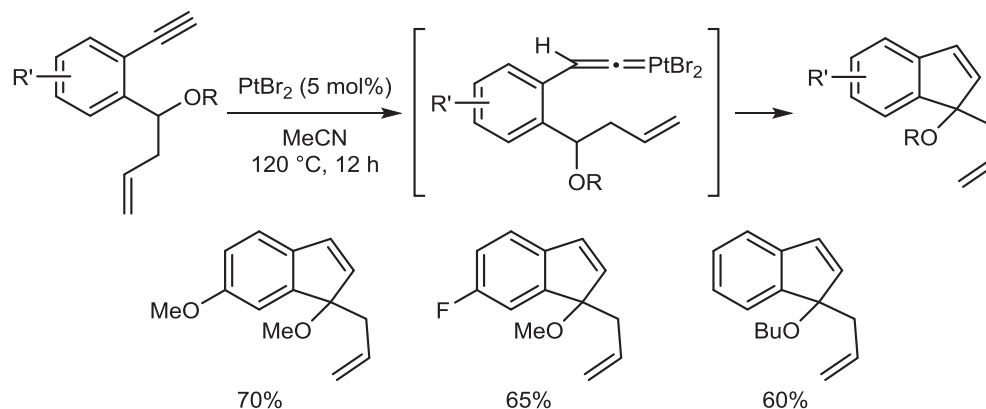
This is a versatile methodology, allowing for introduction of functionalities which may otherwise be difficult to incorporate. For example, Stang reported the synthesis of cyclic vinyl azide **96**

through the treatment of alkynyliodonium tosylate **95** with sodium azide (Scheme 47).⁷⁴

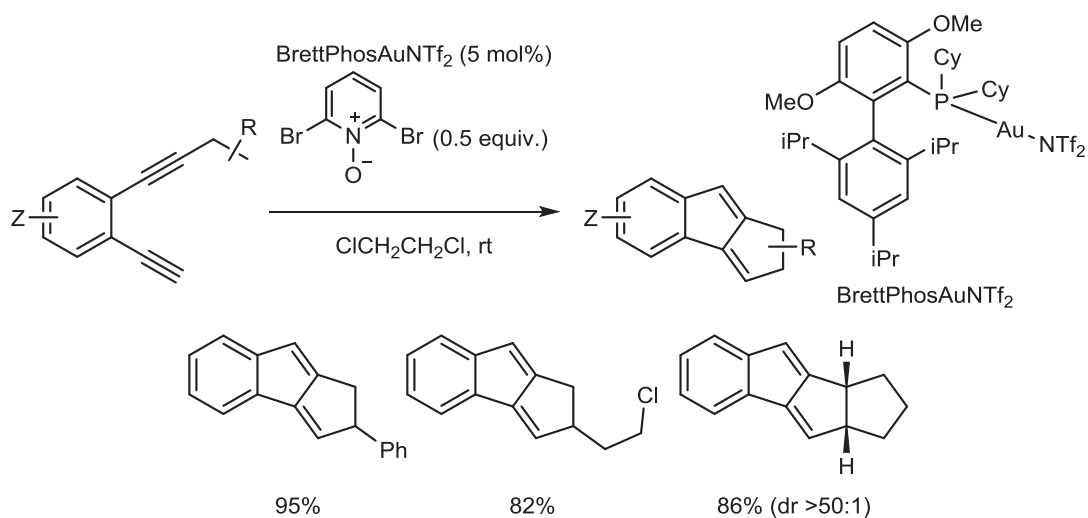
A wide range of other nucleophiles have been used in intermolecular reactions to generate alkylidene carbenes from alkynyliodonium salts, including sulfonamides,^{32b} phenoxides,⁷⁵ sulfinates,⁷⁶ 1,3-dicarbonyls,⁷⁷ tropolone,⁷⁸ thiocyanates,⁷⁹ tellurides and selenides.⁸⁰

This methodology has been developed by Wipf for the synthesis of 1,3-thiazoles, employing thioamides as the nucleophile with alkynyliodonium mesylates (Scheme 48).⁸¹

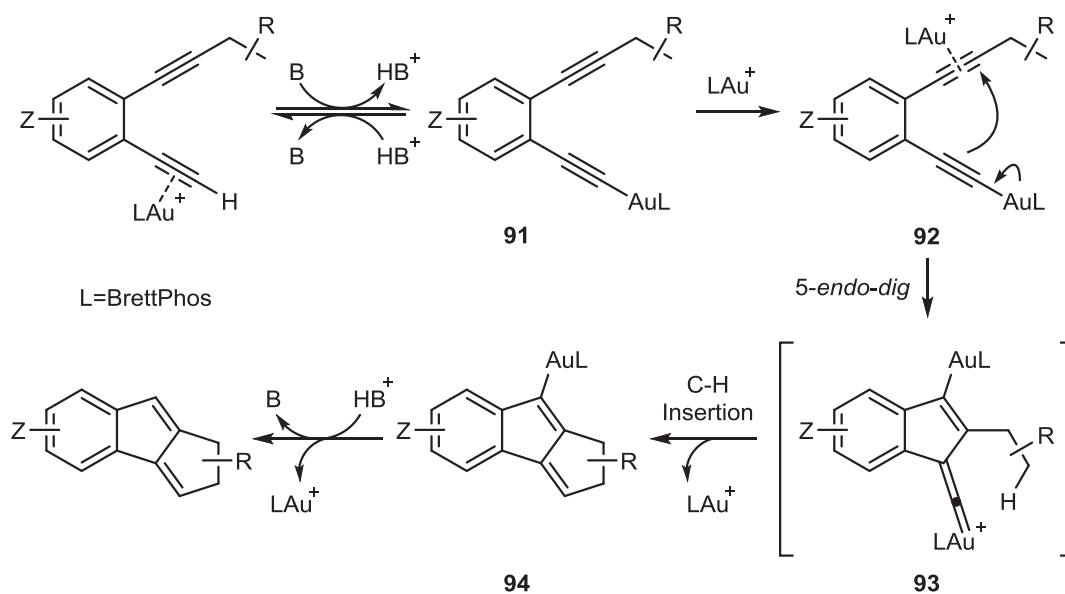
While Wipf proposed two possible mechanisms,⁸¹ Ochiai later demonstrated that the reaction proceeded through initial Michael addition of the thioamide to the alkynyliodonium salt, to afford the alkylidene carbene **97**, which underwent a subsequent 1,2-



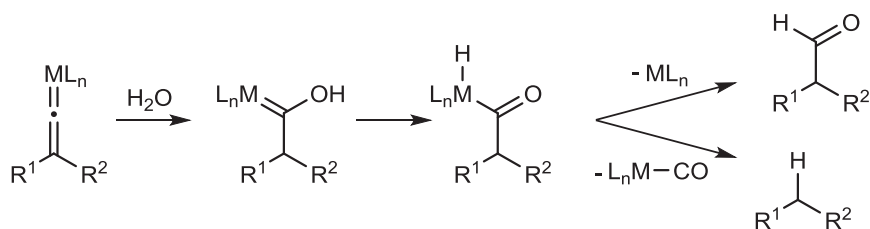
Scheme 40.



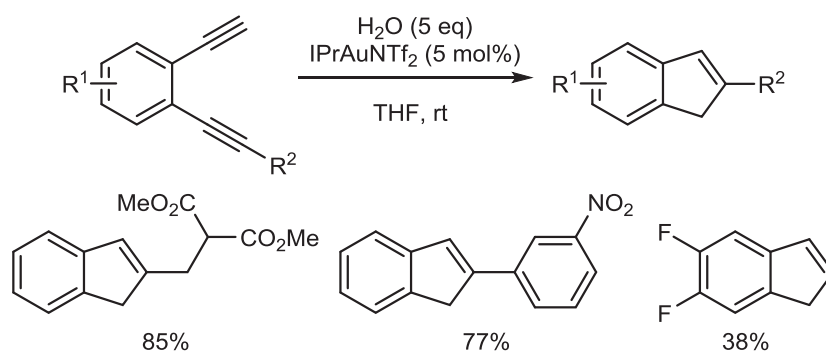
Scheme 41.



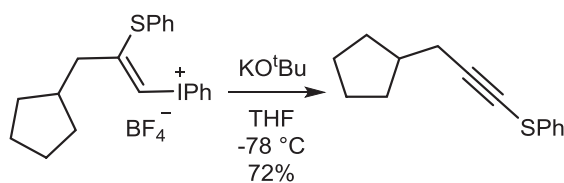
Scheme 42.



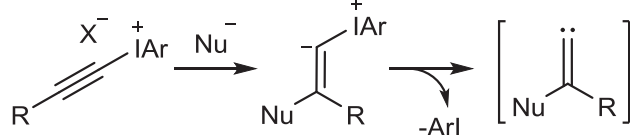
Scheme 43.



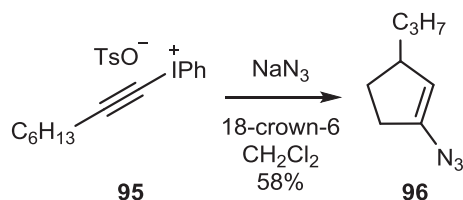
Scheme 44.



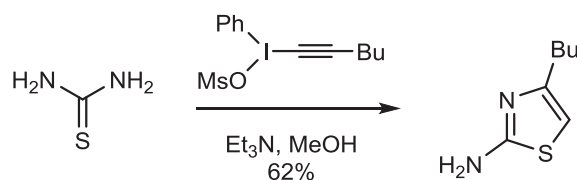
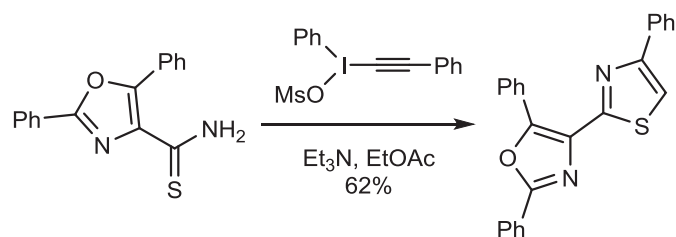
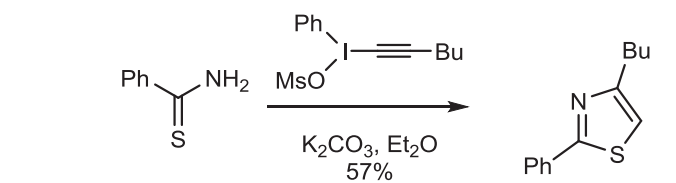
Scheme 45.



Scheme 46.



Scheme 47.



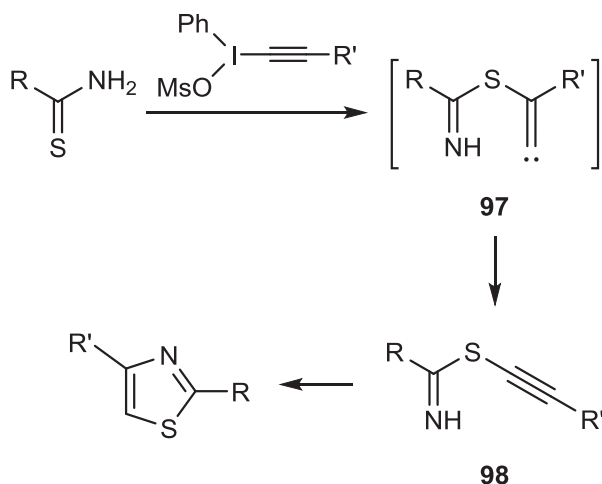
Scheme 48.

migration to form alkyne **98**. This alkyne then undergoes a 5-*endo-dig* cyclization to form the thiazole (Scheme 49).⁸²

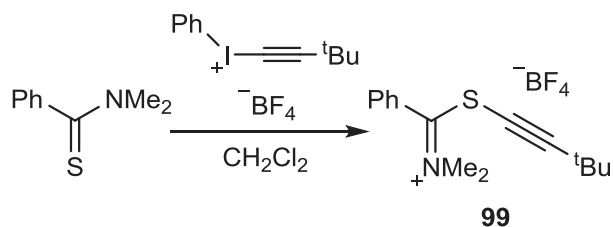
Ochiai proposed that the known migratory aptitude of sulfenyl groups made this mechanism feasible,⁷¹ and was able to provide evidence of this mechanism by performing the reaction with *N,N*-dimethylthiobenzamide. After the proposed alkyne formation, the thiobenzimidonium salt **99** generated would be unable to cyclize and its isolation provided strong evidence for **98** being an intermediate in thiazole formation (Scheme 50).

Kitamura reported the alkylation of benzotriazole with alkynyl-iodonium triflates, where the initial conjugate addition is followed by 1,2-migration of the intermediate alkylidene carbene (Scheme 51).⁸³

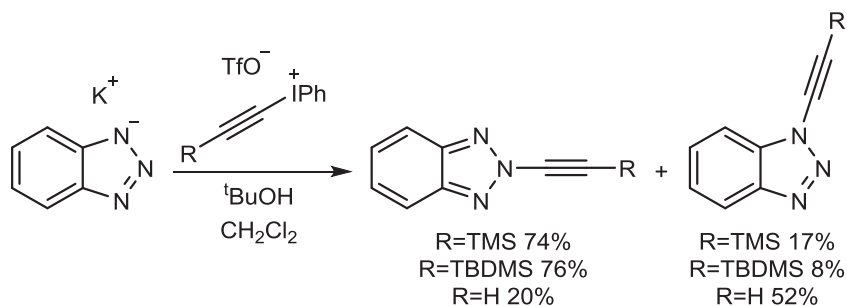
There is a preference for alkylation at *N*-2 with the silylated alkynes, and at *N*-1 in the absence of silicon, believed to be due to unfavourable steric interaction between the benzotriazole and the silyl group, or iodonium substituents, in the event of nucleophilic attack from *N*-1 (Fig. 6). These interactions are minimized in attack at *N*-2. Such interactions are absent in the terminal alkyne, and so attack from *N*-1 is preferred.



Scheme 49.



Scheme 50.



Scheme 51.

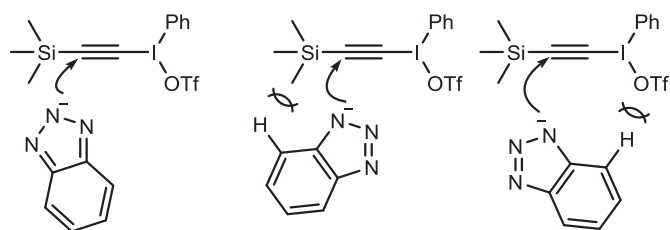
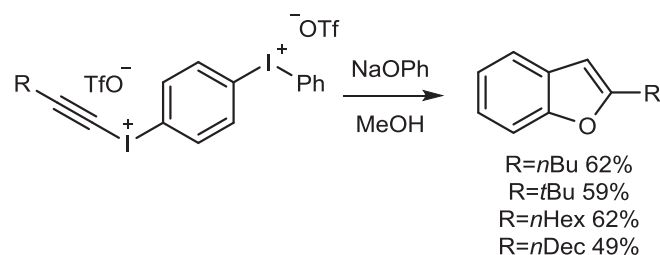


Fig. 6.

The use of alkynyliodonium salts has also led to the discovery of new alkylidene carbene reactivity. It has been demonstrated that the 1,5 C–H insertion is not limited to sp^3 carbon centres.^{75,78,84} Kitamura reported the formation of benzofuran systems upon treating alkynyliodonium salts with sodium phenoxide (Scheme 52).^{84b}

It is interesting to note that the formation of benzofurans is preferred over insertion into the alkyl side chain, with no formation of cyclic enol ethers seen. This selectivity is believed to be due to an interaction between the empty p orbital of the alkylidene carbene



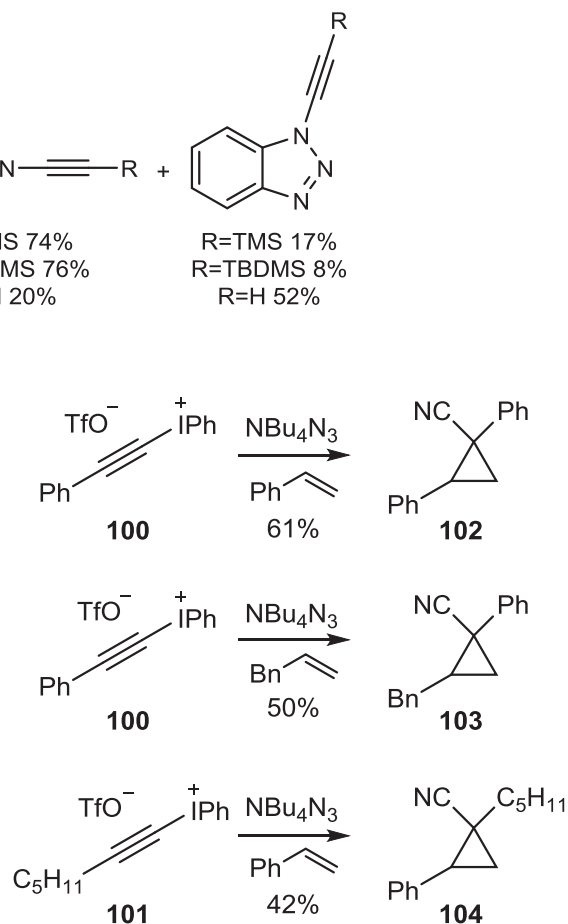
Scheme 52.

and the π -system of the aromatic ring, resulting in aromatic 1,5 C–H insertion becoming more favourable than aliphatic 1,5 C–H insertion.^{84b}

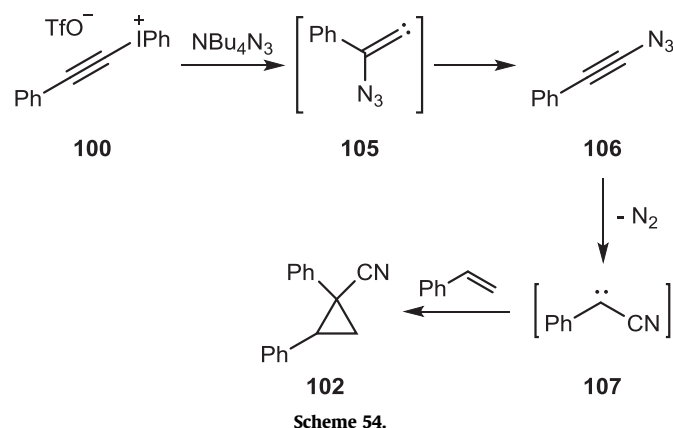
Croatt described the generation of cyanocarbenes via an intermediate alkylidene carbene.⁸⁵ Treating alkynyliodonium salts **100** and **101** with tetrabutylammonium azide gave rise to cyanocyclopropanes **102–104** after reaction with the alkene solvent (Scheme 53).

The reaction is thought to proceed through initial formation of the alkylidene carbene **105** via nucleophilic attack on the β -position of the alkynyliodonium species, as described previously. Subsequent 1,2-migration results in the formation of alkynyl azide **106**, which extrudes N_2 to form the cyanocarbene **107**. This is then trapped by the alkene to give the cyclopropane **102** (Scheme 54).

Feldman reported formal 1,5 C–O insertion in the reaction between alkynyliodonium salts **108** and sodium *para*-toluenesulfonate (Scheme 55, Table 2).^{26b,76b} The reaction is believed to proceed via



Scheme 53.



oxonium ylide interfered with the desired 1,2-shift. In addition, the reactions of **108d** and **108e** suggest that the migration occurs largely with retention of absolute configuration.

Intramolecular nucleophilic attack to form alkylidene carbenes from alkynyliodonium salts has also been reported.⁵⁷ Examples will be discussed in the section on diastereoselectivity.

There are a number of methods that can be employed in order to synthesize alkynyliodonium salts.^{77c,86} The most commonly employed route is the reaction of alkynylstannanes with Stang's reagent (PhI(CN)OTf).^{86g,h} This method allows for the synthesis of alkynyliodonium triflates incorporating a range of functionalities including alkyl, aryl, heteroaryl, halogens, carbonyls and sulfones, in yields ranging from 42% to 89%.^{86h} However, a major drawback of the route is the release of stoichiometric HCN. In addition, it is also necessary to prepare Stang's reagent prior to use.^{29c,30b,77c,87} Alternative routes have been developed that allow for the synthesis of

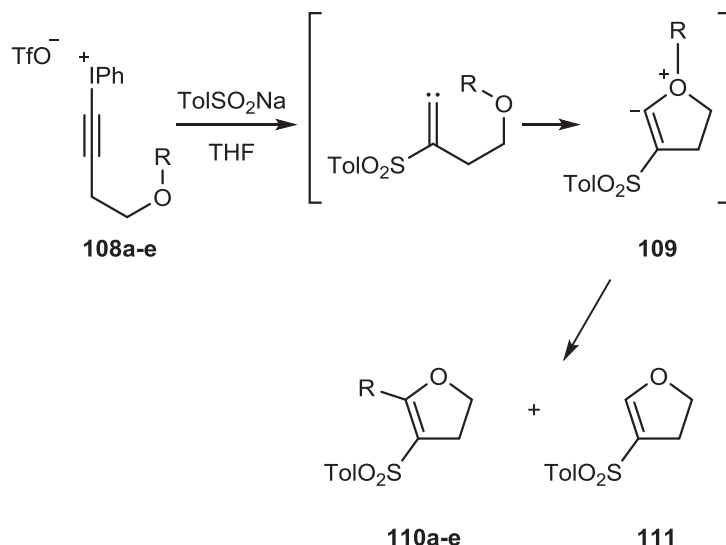


Table 2

	R	110 (%)	111 (%)
a	TBS	65	—
b	Allyl	—	36
c	Benzyl	—	19
d		41 (8.5:1 dr)	16
e		43 (10:1 dr)	16

initial oxonium ylide **109** formation followed by subsequent migration to give the disubstituted dihydrofurans **110**. Feldman reported that only groups, which offered substantial carbocation stabilization underwent migration, as evidenced by the lack of reaction of benzyl and allyl ethers. In addition, a significant amount of the protonated dihydrofuran **111** was observed in most cases.

The formation of **111** in the reaction of **108c** suggested that the oxonium ylide **109** was formed but reacted via a different pathway other than the desired migration. In particular, the isolation of small quantities of *p*-TolSO₂CH₂Ph suggested nucleophilic attack α to the

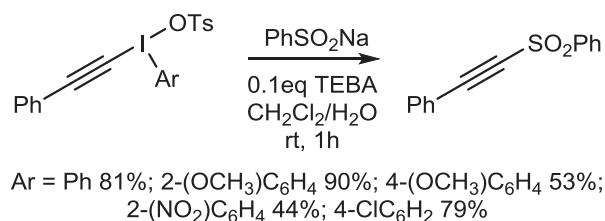
alkynyliodonium salts using PhI(OAc)₂ in the presence of TfOH, Tf₂O or TFA.⁸⁸ These developments have also allowed for the use of alkynylsilanes and terminal alkynes instead of alkynylstannanes.

Olofsson reported the synthesis of alkynyliodonium salts directly from terminal alkynes⁸⁹ and alkynyl boronates.⁹⁰ Moran used this methodology to explore the effect of the aromatic iodine species on migration and insertion reactions of alkylidene carbenes.⁹¹ Superior results were achieved using a 2-anisyl substituent (Scheme 56). These results can be contrasted with those of Carroll,^{88b} who reported altering the aromatic substituent had minimal effect on the 1,5 C–H insertion into an aromatic system. As part of the same study, Moran reported that altering the counter ion had no discernible effect on the formation of alkynyl sulfones.⁹¹

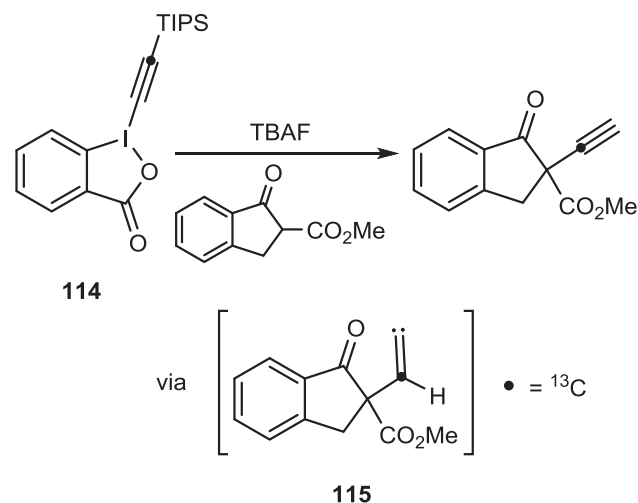
Waser reported the use of ethynyl-1,2-benziodoxol-3(1*H*)-one **113** (EBX) as a reagent for the alkylation of electron-deficient esters.⁹² EBX was generated in situ by treating TMS-EBX **112** with TBAF. Subsequent reaction with the ester led to α -alkynylation (Scheme 57). TBAF also acts as a base within the reaction.

TMS-EBX **112** can be prepared simply by partial oxidation of 2-iodobenzoic acid with NaIO₄, followed by reaction with bis(trimethylsilyl)acetylene in the presence of TMSOTf.⁹³

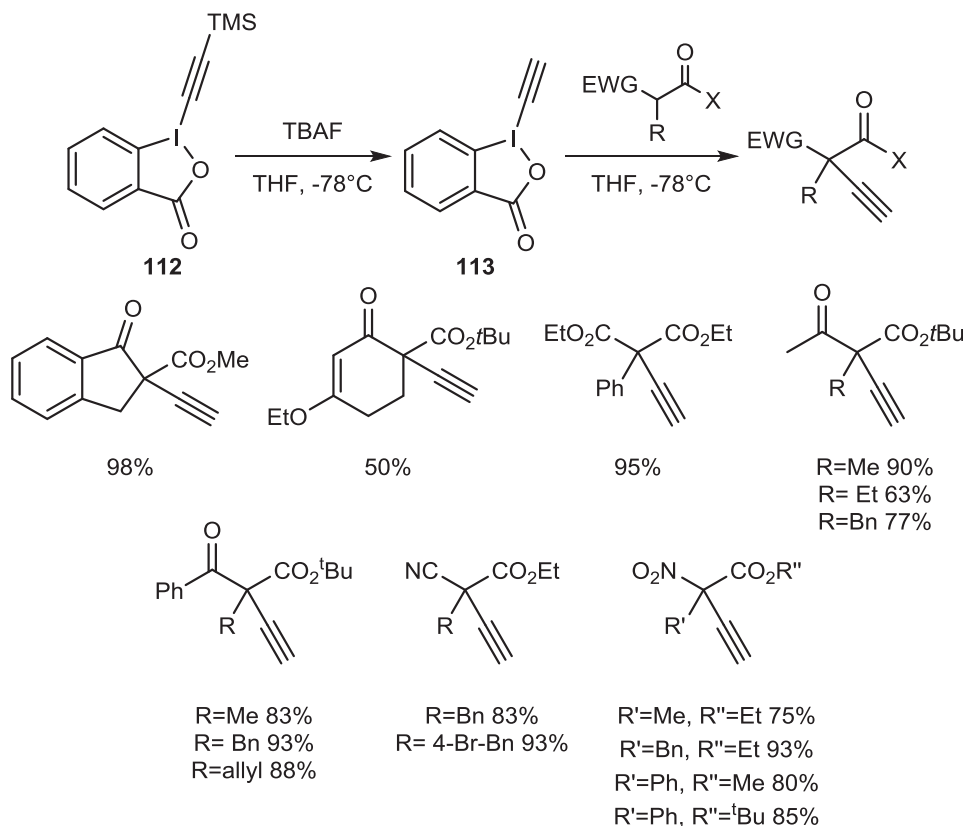
The reaction was shown to proceed through an alkylidene carbene by the use of ¹³C labelling (Scheme 58). By labelling the alkyne carbon bonded to the silicon in TIPS-EBX **114**, and determining its presence in the final product as being directly bonded to the α -position of the ketone, it suggests that initial nucleophilic attack



Scheme 56.



Scheme 58.



Scheme 57.

occurs on the β -carbon of the alkynyliodonium species, leading to alkyldene carbene **115**. This also suggests that the hydrogen undergoes migration to form the final product.

This reaction has been rendered asymmetric, albeit with modest enantioselectivity, through use of a chiral phase transfer catalyst.⁹²

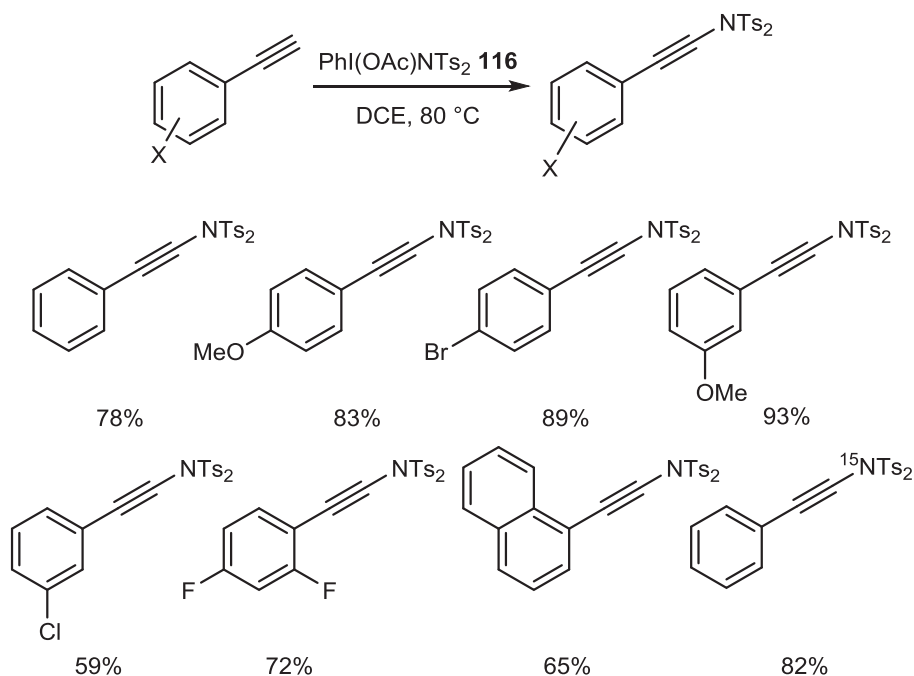
TIPS-EBX **114** has also been used for the synthesis of alkynyl sulfides,⁹⁴ although the mechanism is not believed to proceed through an alkyldene carbene intermediate.⁹⁵

While the use of alkynyliodonium salts has allowed for the synthesis of cyclopentenes and alkynes with a wide range of functionalities, it usually requires the pre-functionalization of an alkyne with the hypervalent iodine. Recently, Muniz has reported the synthesis of ynamides and cyclic enamides from terminal

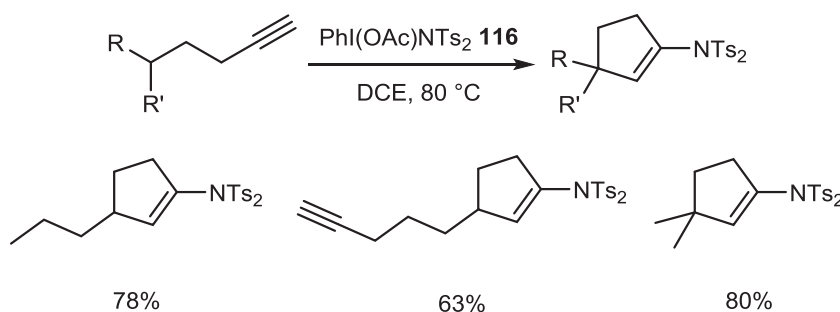
alkynes using a range of iodine(III) reagents, which are readily available from PhI(OAc)_2 .⁹⁶ The reaction was shown to be successful in synthesizing a range of bis-tosyl ynamides from the corresponding acetylenes, using hypervalent iodine reagent **116** (Scheme 59).

The methodology has also been applied to the synthesis of cyclic enamides. Treating alkyl alkynes with **116** gave cyclization products in good yields (Scheme 60).

The proposed mechanism is as follows: the initial coordination of the electrophilic iodine(III) to the alkyne, forming complex **117**, increases the acidity of the alkyne C–H bond. Deprotonation of the alkyne leads to alkynyliodonium **118**. Nucleophilic attack on the β -carbon by the tosylamide anion, results in alkyldene



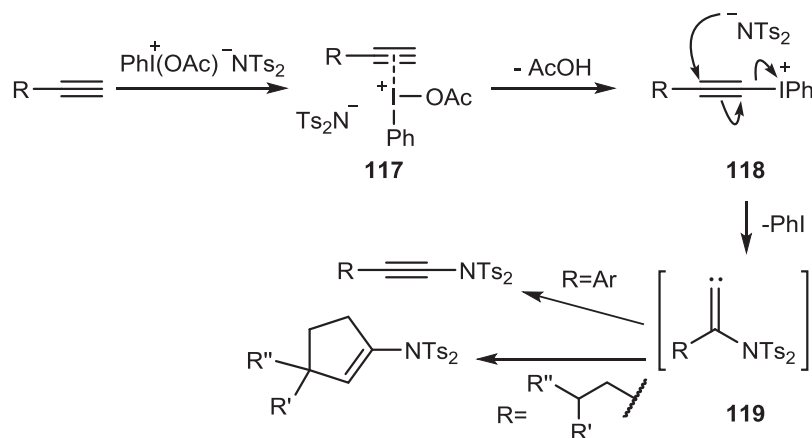
Scheme 59.



Scheme 60.

carbene **119**, with concurrent loss of PhI . From here, 1,2-migration or 1,5-insertion occurs, depending on the substituent on the alkylidene carbene, leading to the observed products (Scheme 61).

The relative ease of access to alkynylidonium species, coupled with the wide range of functionalities that can be incorporated into the alkylidene carbenes generated from them, makes them important reagents in the use of alkylidene carbenes in organic



Scheme 61.

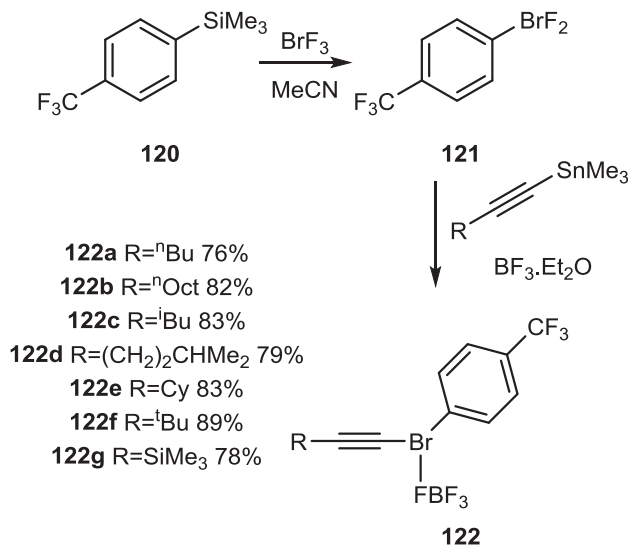
synthesis. The work of Kitamura and Carroll has allowed for the generation of these versatile reagents under milder, safer conditions, while the recent developments by Muniz have allowed for the in situ generation and reaction of alkylidene carbenes directly from the terminal alkyne, eliminating the need to prepare alkynylstannanes or alkynyliodonium species.

3.5. Hypervalent bromine

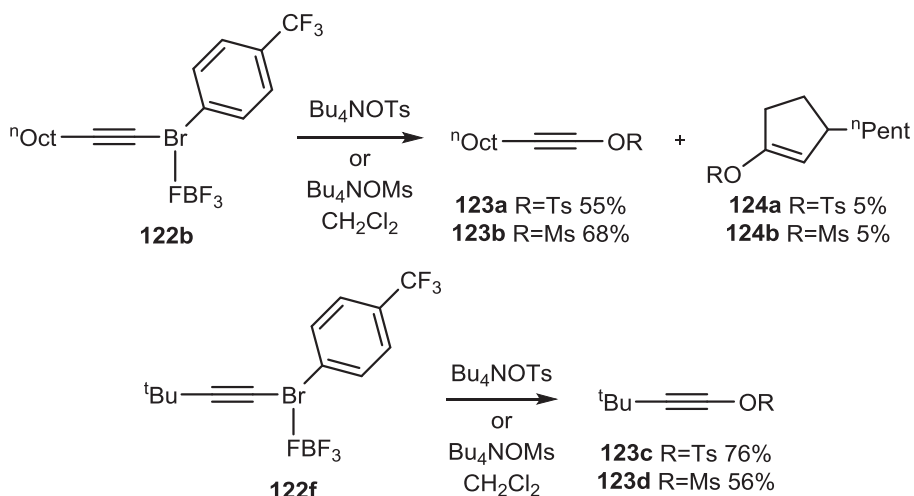
Expansion on the extensive work carried out on alkynyliodonium species as alkylidene carbene precursors has led to the investigation of the use of related alkynylbromonium, or 1-alkynyl(aryl)- λ^3 -bromane, substrates in a similar fashion.⁹⁷ λ^3 -Bromanyl groups have a greater Hammett substituent constant than the equivalent λ^3 -iodanyl ($\sigma_p=1.63$ for PhBrBF₄ compared to $\sigma_p=1.37$ for PhIBF₄), suggesting that 1-alkynyl- λ^3 -bromanes may be better Michael acceptors.⁹⁸

Ochiai reported the synthesis of a number of alkynylbromonium tetrafluoroborates. Treatment of aryl silane **120** with BrF₃ gave rise to **121**, which subsequently reacted with alkynylstannanes to give the alkynylbromonium tetrafluoroborates **122a–g** (Scheme 62).⁹⁹

Like the hypervalent iodine reagents described above, alkynylbromonium reagents undergo reaction with sulfonate nucleophiles



Scheme 62.



Scheme 63.

to give the corresponding cyclopentenones.¹⁰⁰ However, Ochiai demonstrated less reactive nucleophiles such as tosylates and mesylates react to give alkynes **123a–d** and cyclopentenones **124a,b** (Scheme 63).⁹⁹ Reaction with weak nucleophiles such as sulfonate anions, shows that these reagents are considerably more reactive than the corresponding iodonium reagents. Sulfonate anions do not react with alkynyliodonium salts.^{74,86e}

The use of sodium trifluoromethanesulfinate (triflate) as a nucleophile gave rise to a mixture of vinyl triflate **125** and alkynyl triflate **126** in good yield. A similar reaction between **127** and sodium triflate gave the bicycle **128** with excellent selectivity (Scheme 64).

The range of nucleophiles that underwent reaction with alkynylbromonium species was expanded to include metallated alkynes. Ochiai reported that treating alkynylstannanes with **121** resulted in an oxidative homocoupling (Scheme 65).¹⁰¹ It is thought that the reaction proceeds through the initial formation of **122**, followed by the formation of bromonium ylide **130** and subsequent elimination to the alkylidene carbene.

The methodology was applied to various alkyne–alkyne oxidative cross-couplings between alkynylbromoniums and various alkynylstannanes to give unsymmetrical diynes.¹⁰¹

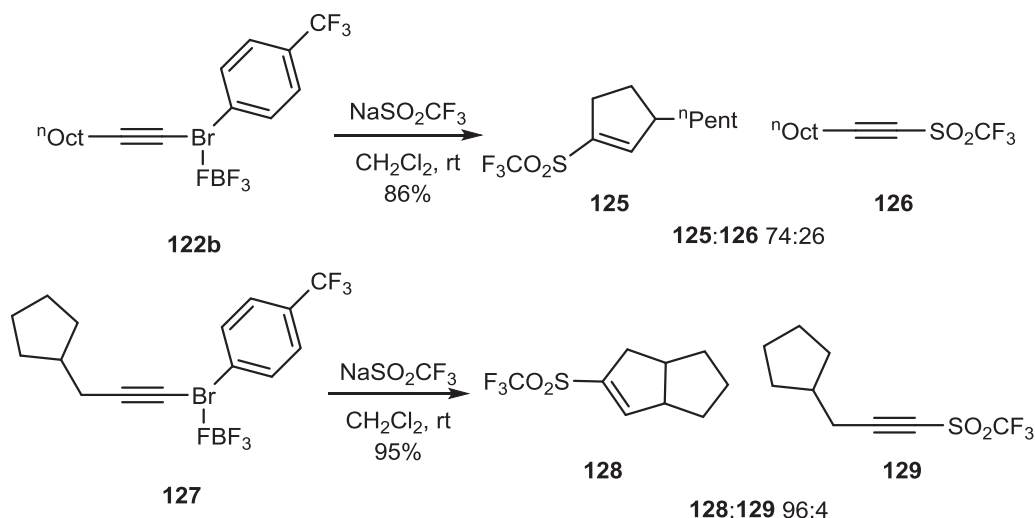
Ochiai also reported the synthesis of alkynyl triflate **131**, by reacting alkynylbromonium **122b** with a large excess of sodium triflate (Scheme 66). This example in particular demonstrates the propensity of alkynylbromonium to act as Michael acceptors, as triflate anions are generally held to be non-nucleophilic in nature.

Alkynylbromonium species holds great promise as alkylidene carbene precursors, particularly in the use of poor nucleophiles such as tosylates and triflates; however, their application is currently limited by the preparation of difluorobromonium reagents, due to the high toxicity and extreme reactivity of the BrF₃ required for their formation.¹⁰²

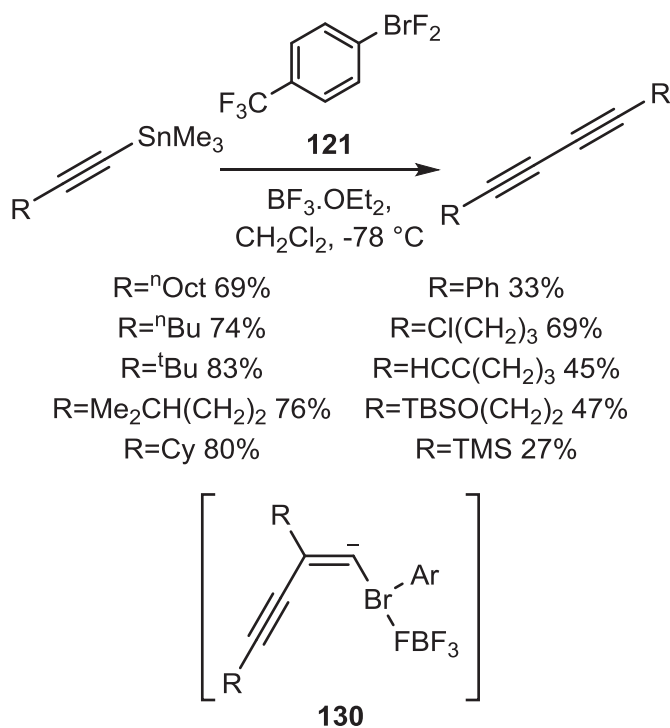
3.6. Vinyl aminosulfoxonium salts

Gais reported the use of chiral vinyl aminosulfoxonium salts as precursors to alkylidene carbenes in the synthesis of enantio-merically enriched homopropargylic alcohols.¹⁰³ Treatment of the salts with base gave the corresponding sulfur ylide **132**, from which loss of sulfonamide **133** gave the alkylidene carbene **134**. Subsequent 1,2-migration gave the chiral homopropargylic silyl ethers **135** (Scheme 67).

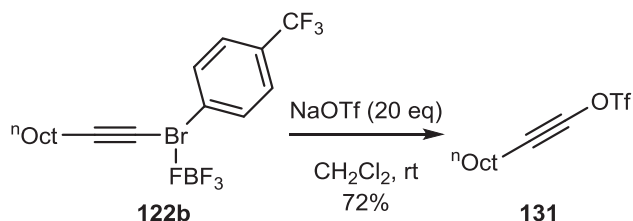
Gais also employed this methodology for the asymmetric synthesis of dihydrofurans **137** via 1,5 O–Si insertion of the



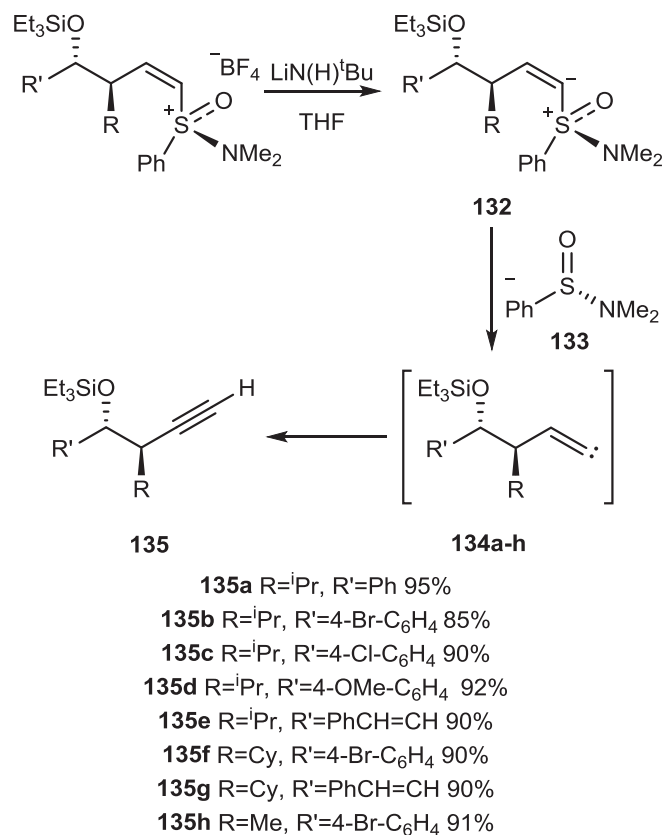
Scheme 64.



Scheme 65.



Scheme 66.



Scheme 67.

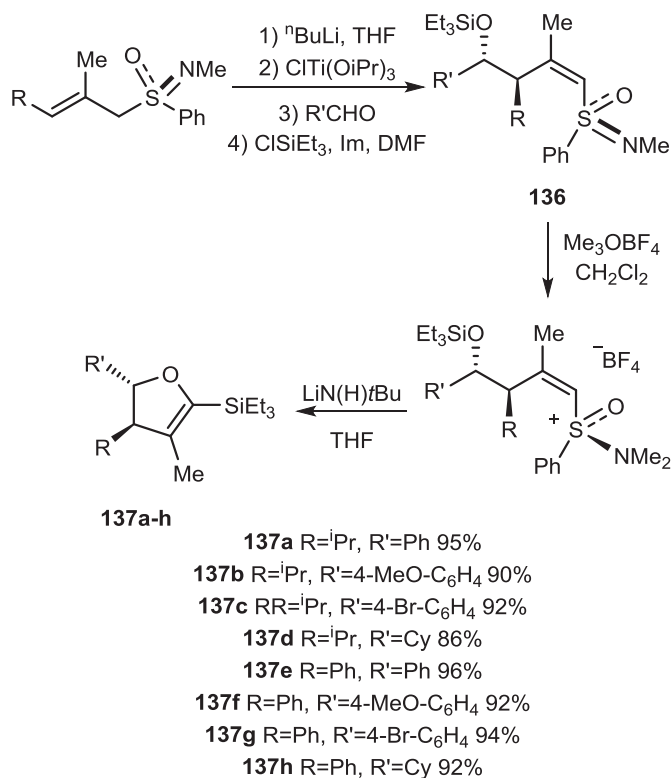
methodology, particularly as the chiral sulfonamide by-product can be recovered in excellent yields (in excess of 85%) and recycled for use in subsequent enantiopure sulfoximine synthesis.¹⁰⁵

4. Chemoselectivity and regioselectivity

4.1. Substrate effects on selectivity

Due to carbenes being strongly electron-deficient, they are highly electrophilic and so react faster with functionalities which

intermediate alkylidene carbene (Scheme 68).¹⁰⁴ The use of a sulfoximine as a both chiral auxiliary (e.g. in the synthesis of 136) and as an alkylidene carbene precursor is an attractive feature of this



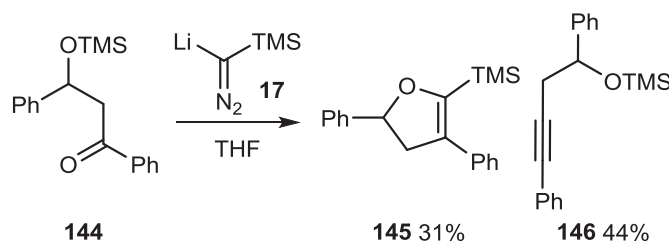
Scheme 68.

are relatively electron-rich. Such is the sensitivity of alkylidene carbenes to these electronic effects, they preferentially undergo 1,5 C–H insertion reactions with tertiary C–H bonds in the presence of less substituted 1,5 C–H insertion sites.¹⁰⁶ The relative rates of reaction have been demonstrated to be 1:30:240 (primary/secondary/tertiary).¹⁰⁶ It has also been shown that heteroatoms adjacent to C–H bonds accelerate reaction at that site.^{10,44e,55a,107}

Insertions into O–Si bonds have been shown to occur faster than C–H insertion reactions, with Kim reporting the formation of dihydrofuran **139** from azirindinylimine **138** with no evidence of **140** seen. However, this is only true for the formation of five-membered heterocycles as employing azirindinylimines **141** in the same reaction gave mainly cyclopentenones **142** via 1,5 C–H insertion, with heterocycles **143a** and **143b**, formed via 1,6 O–Si insertion and 1,7 O–Si insertion, respectively, isolated in only low yields (Scheme 69).^{26a}

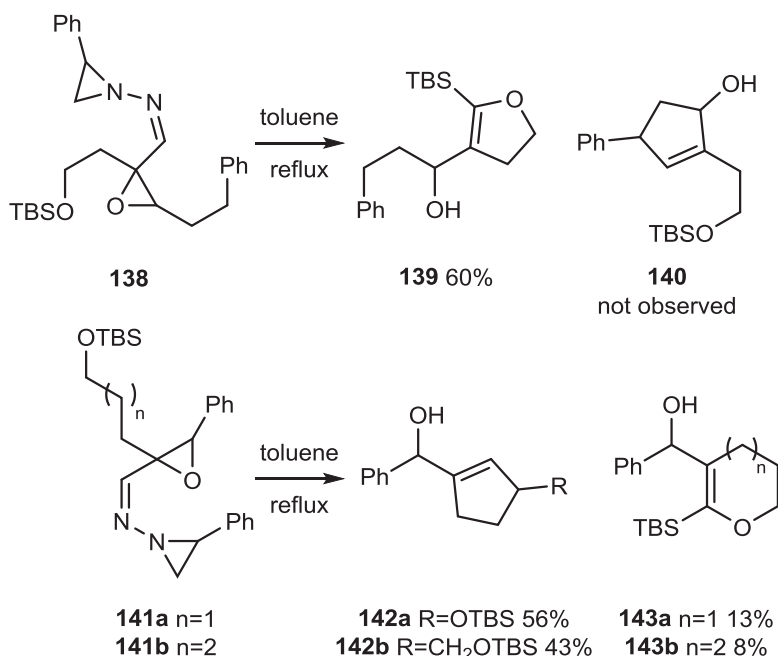
Feldman has also demonstrated that the formation of five-membered heterocycles via formal insertions into heteroatom–hydrogen bonds, occurs in preference to competing 1,5 C–H insertion reactions.¹⁰⁸

While alkylidene carbenes bearing aryl substituents usually undergo 1,2-migration reactions in preference to 1,5 C–H insertion reactions, Shioiri²⁵ demonstrated that 1,5 O–Si insertion reactions can compete with the migration of phenyl groups, as shown by the reaction of lithiated trimethylsilyldiazomethane **17** with ketone **144** giving a mixture of dihydrofuran **145** and alkyne **146** (Scheme 70).²⁵ Shioiri²⁵ and Kim^{26a} both reported that 1,2 hydrogen migration occurs in preference to 1,5 O–Si insertion.



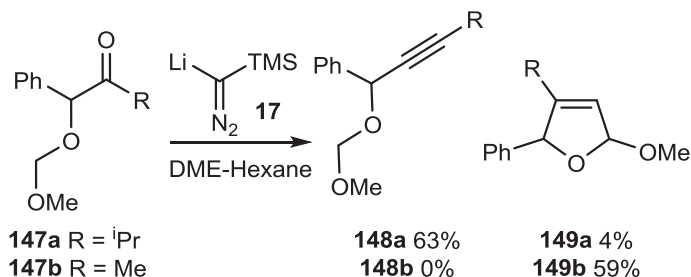
Scheme 70.

Despite the tendency for alkyl-substituted alkylidene carbenes to undergo insertions reactions, Wills demonstrated that it is possible for 1,2-alkyl shifts to occur and even predominate.¹⁰⁹ The reaction of ketone **147a** with lithiated trimethylsilyldiazomethane **17**



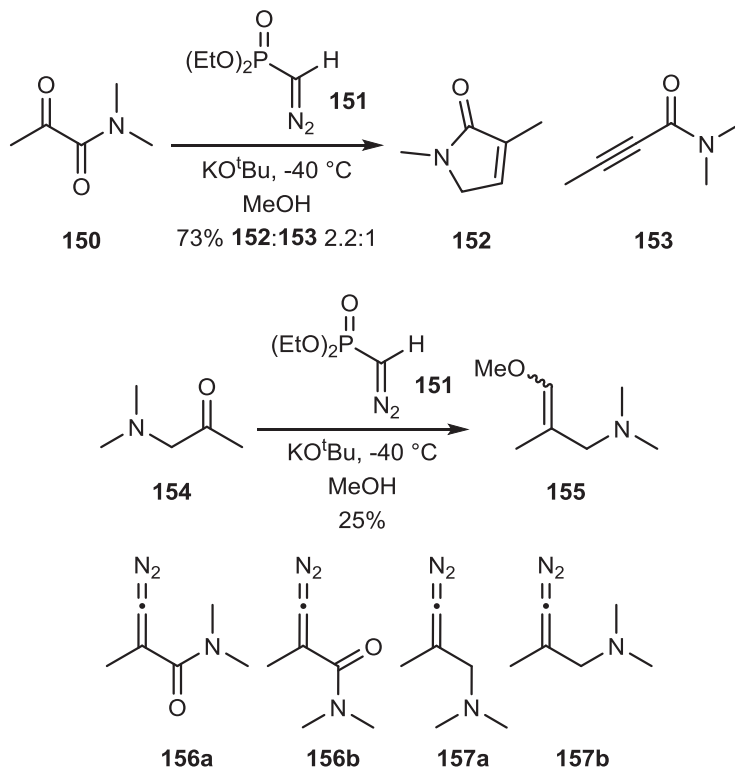
Scheme 69.

gave alkyne **148a** as the major product with the corresponding dihydrofuran **149a** isolated in only low yield (Scheme 71). The methyl ketone **147b** gave the dihydrofuran **149b** exclusively, and it was postulated that the increased electron-donating capabilities of the isopropyl group resulted in its preferential migration to form the alkyne.¹⁰⁹



Scheme 71.

Substrate effects can also have a significant influence on alkylidene carbene insertion reactions. Gilbert reported interesting chemo- and regioselectivity in the reactions of several nitrogen-containing ketones with DAMP **151**.¹¹⁰ α -Amidoketone **150** gave rise to 3-pyrrol-2-one **152** along with butynamide **153**. In contrast, reacting α -aminoketone **154** under the same conditions gave methyl enol ether **155** as the main product, where the intermediate alkylidene carbene is quenched by the solvent (Scheme 72).



Scheme 72.

Gilbert proposed that diazoalkene **156**, from the initial Horner–Wadsworth–Emmons reaction between **150** and **151**, would be close to planar in order to maintain π -delocalization throughout the system. Rationalizing that the *s-trans* conformation **156a** would be more favourable than the *s-cis* **156b**, due to decreased

dipole–dipole interactions, this would result in an alkylidene carbene with a suitable C–H insertion site in close proximity. Conversely, due to more favourable steric interactions, the more conformationally flexible diazoalkene **157** is likely to exist in a conformation such as **157a**, which lacks a proximal site for C–H insertion, allowing intermolecular reaction with the solvent to dominate (Scheme 72).

Performing the reaction on unsymmetrically substituted amides gave a mixture of 3-pyrrol-2-ones **159** and **160**, with insertion into the *N*-methyl group preferred over insertion into the *N*-methylene, along with ynamides **161** (Scheme 73).¹⁰⁶

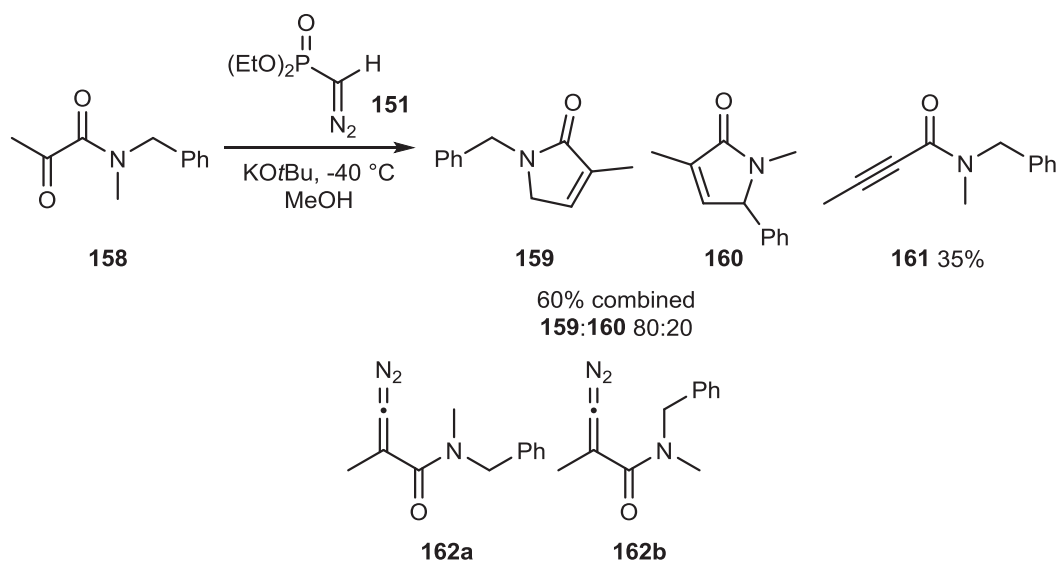
The reaction between **158** and **151** leads to diazoalkene **162**, which can exist in two rotameric forms, both of which are in a suitable conformation for efficient C–H insertion (Scheme 73). Gilbert proposed that the increased steric hindrance between the larger *N*-alkyl substituent and the diazoalkenyl group resulted in **162b** being less favoured, allowing insertion into the primary C–H bond to dominate, and hence the reverse of typical selectivity.

Grainger and Owoare reported preferential C–H insertion over the normally favoured O–Si insertion in synthesizing tetracycle **164** from vinyl chloride **163** (Scheme 74).¹¹¹

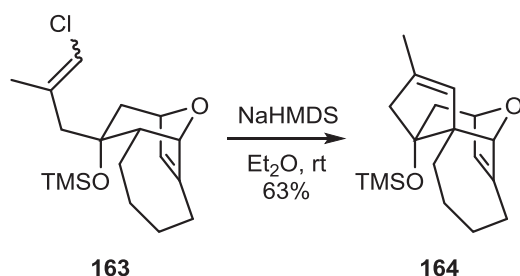
It was proposed that in order for O–Si insertion to occur, there must be an interaction between the oxygen lone pair and the empty p-orbital on the alkylidene carbene. In this example, the bulky TMS group is expected to be orientated *exo* to the ring system in order to minimize any unfavourable steric interactions, as in **165**. This would result in both oxygen lone pairs sitting in an *endo* orientation, unable to interact with the empty p-orbital. In order to achieve the necessary orbital overlap, the molecule must adopt a much higher

energy conformation, such as **166** or **167** (Scheme 75). As a result, the 1,5 C–H insertion pathway dominates.

However, further work on the reactivity of alkylidene carbenes on 8-oxabicyclo[3.2.1]oct-6-ene systems by Grainger and Munro demonstrated that this selectivity was not absolute. A comparison



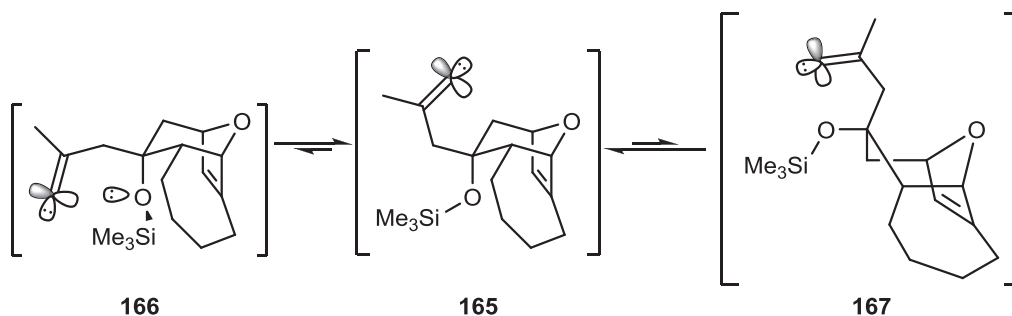
Scheme 73.



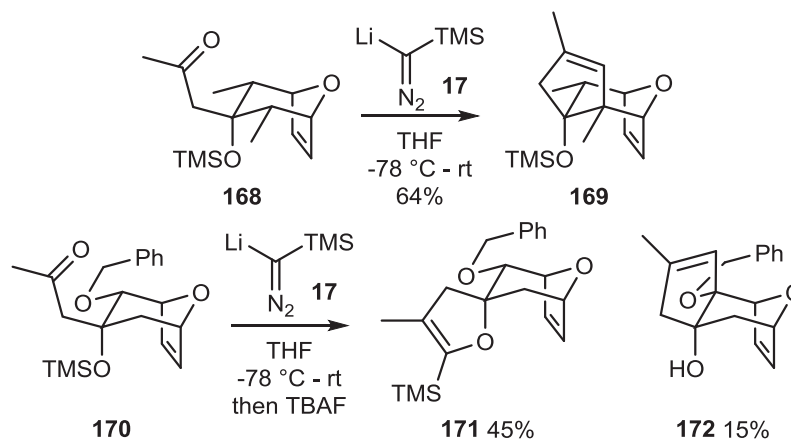
Scheme 74.

of the 2,4-dimethyl-substituted **168** and the 2-benzyloxy **170** ring systems showed that their structural features can dramatically affect selectivity.^{55b} Reaction of ketone **168** with **17** afforded cyclopentene **169** as the exclusive product. However, reacting ketone **170** under the same conditions gave a 3:1 mixture of dihydrofuran **171** and cyclopentene **172** after O-desilylation (Scheme 76).

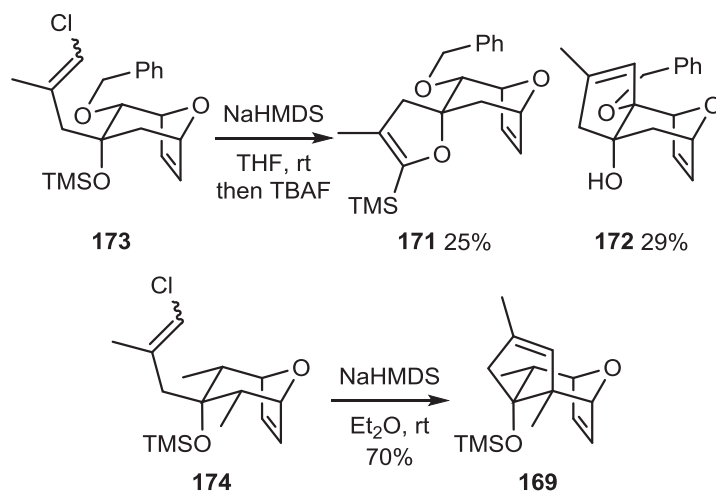
As expected, the 2-benzyloxy group controls the regioselectivity of the C–H insertion reaction; however, its introduction also leads to O–Si insertion. Moreover, the ratio of C–H insertion to O–Si insertion is contingent on the method employed to generate the alkylidene carbene. The reaction of vinyl chloride **173** with



Scheme 75.



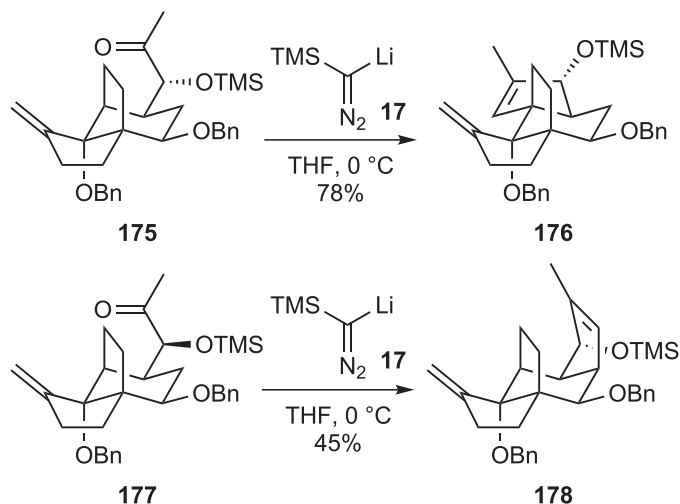
Scheme 76.



Scheme 77.

NaHMDS gave the same mixture of products, this time in a ~1:1 ratio (Scheme 77).^{55b} The reaction of the dimethyl analogue **174** again gave cyclopentene **169** as the only product.¹¹¹ The change in product ratio in the reactions of **170** and **173** can be attributed to the nature of the carbene generated; **170** leads to a reactive free alkylidene carbene as opposed to the less reactive carbenoid formed from **173** (vide infra), however, it is unclear why such a drastic change in reactivity occurs upon the introduction of the benzyloxy substituent. Further examples of the effects of reaction conditions on the selectivity of alkylidene carbenes will be discussed later in this review.

H.-Y. Lee has shown that it is possible to override the preference for alkylidene carbenes to insert into tertiary C–H bonds over secondary C–H bonds (Scheme 78).¹¹² The alkylidene carbene generated from ketone **175** was shown to react exclusively with the tertiary C–H bond giving tetracycle **176** in good yield. However, the epimer **177** shows preferential insertion into the secondary C–H bond, giving **178**. H.-Y. Lee suggested that an unfavourable steric interaction between the OTMS group and the ring system in **177** disfavours the conformation for insertion into the tertiary C–H bond, allowing insertion to occur at the electronically less favoured methylene site.



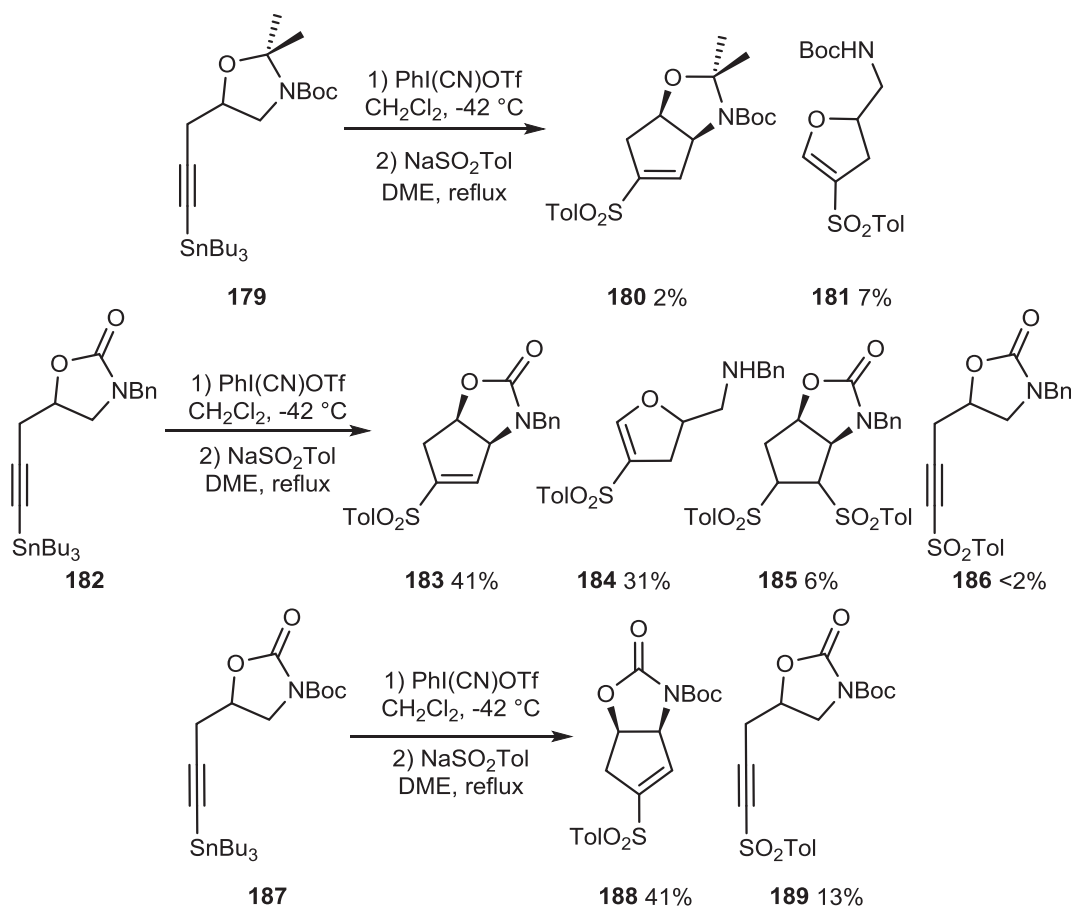
Scheme 78.

Feldman demonstrated how the reactivity of the intermediate alkylidene carbene could be controlled through substrate modification (Scheme 79).¹¹³ Treatment of alkynylstannane **179** with Stang's reagent, followed by reaction of the crude iodonium salt with NaSO_2Tol , gave a mixture of vinyl sulfone **180** and dihydrofuran **181** (formed via initial reaction between the alkylidene carbene and the oxygen lone pair) in poor yield, with **181** as the major product.¹¹³

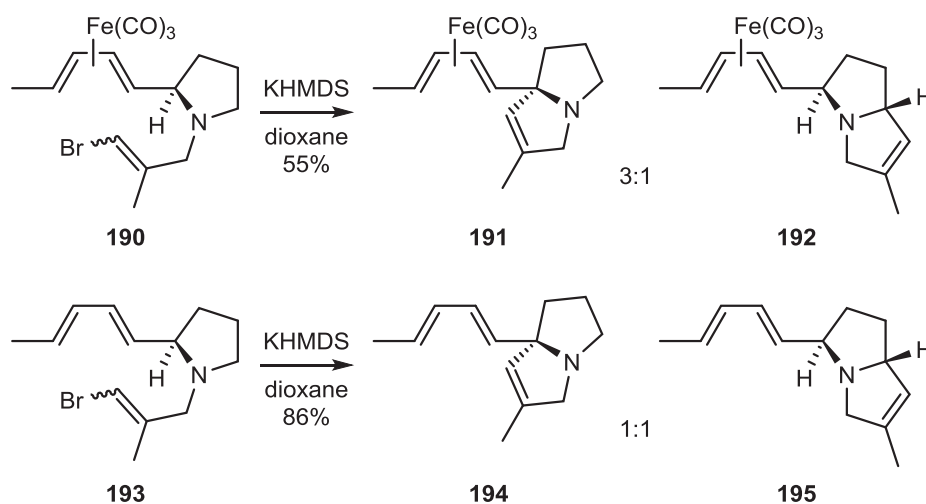
It was postulated that replacing the *gem*-dimethyl group with a more electron-withdrawing substituent would reduce the reactivity of the oxygen lone pairs towards the alkylidene carbene, allowing the desired C–H insertion reaction to occur preferentially. Thus, alkynylstannane **182** was synthesized and subjected to the same reaction conditions, leading to a mixture of products. Feldman proposed that bis-sulfone **185** arose from vinyl sulfone **183**, and so the ratio of C–H insertion to reaction at oxygen had increased from 1:3 to 1.5:1. Alkynylsulfone **186** was also isolated in low yield.

When the *N*-benzyl substituent in **182** was replaced with *N*-Boc a mixture of vinyl sulfone **188** and alkynylsulfone **189** was isolated. Feldman proposed that employing the electron-withdrawing Boc group results in the nitrogen lone pair being delocalized primarily into the carbamate moiety, and the oxygen lone pair being delocalized into the oxazolidinone carbonyl. As such, the oxygen lone pair is less available to interact with the alkylidene carbene, suppressing reaction at oxygen. However, the introduction of the Boc group most likely accounts for the increased formation of **189**, as the C–H bond at which insertion is desired is now more electron-deficient and so C–H insertion occurs more slowly, allowing the normally slower 1,2-sulfonyl shift to compete.¹¹³

Cox reported an interesting change in regioselectivity of a 1,5 C–H insertion reaction adjacent to nitrogen upon decomplexation of a $\text{Fe}(\text{CO})_3$ moiety from a tethered diene (Scheme 80).¹¹⁴ Performing the reaction on the iron complex **190** gave a mixture pyrrolizidines **191** and **192** in moderate yield, with preferential insertion into the tertiary C–H bond. However, reaction of the free diene **193** led to a 1:1 mixture of **194** and **195** in better yield. Cox postulated that the $\text{Fe}(\text{CO})_3$ group led to increased steric crowding of the methine C–H bond, resulting in a longer and weaker bond. He also suggested that anchimeric assistance from the iron complex would electronically activate the tertiary C–H bond towards insertion, resulting in improved regioselectivity. Both **192** and **195** were formed diastereoselectively, with the diene substituent on the *exo* face of the [3.3.0] bicyclic ring system.



Scheme 79.



Scheme 80.

Although preferential insertion into C–H bonds adjacent to heteroatoms was well known in the literature prior to 2009, a comprehensive study by D. Lee and co-workers clearly demonstrated that 1,5 C–H insertion reactions adjacent to oxygen are subject to a subtle combinations of steric, electronic, conformational and stereoelectronic effects.¹¹⁵ Indeed, in a systematic study of reactions of lithium trimethylsilyldiazomethane **17** with various oxygenated ketones, it was shown that the preference for C–H

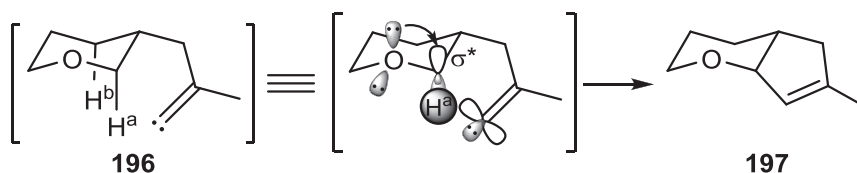
insertion next to oxygen could in fact be overridden. The following conclusions could be made:

- While adjacent oxygen atoms increase the rate of 1,5 C–H insertion, this is more pronounced in systems where the oxygen atom is part of the newly formed ring system.
- The increased activation of endocyclic oxygen is relatively subtle and the use of mildly electron-withdrawing substituents

can diminish its effect, allowing competing insertion next to exocyclic oxygen atoms to dominate.

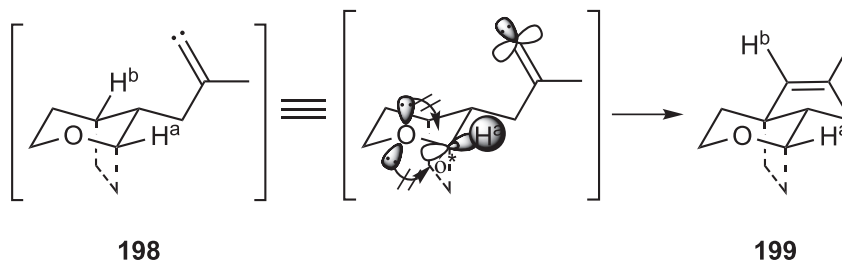
- 1,5 C–H insertion into more conformationally constrained systems is slower than reaction in more flexible systems.
- 1,5 C–H insertion does not occur into the C–H of an epoxide.
- The steric environment of the C–H bond undergoing insertion can affect the rate at which reaction occurs. However, these effects are less significant than electronic and conformational effects.

Of particular note is how stereoelectronic effects influence the selectivity of 1,5 C–H insertion.¹¹⁵ In alkylidene carbene **196**, D. Lee proposed that the most important orbital interaction would be between the axial non-bonding orbital of the oxygen and the σ^* orbital of the axial C–H^a bond. If this stereoelectronic effect was important, **196** should give **197** as the major product, via selective insertion into the axial C–H^a bond as this would be more electron-rich in nature due to $n(\text{O}) \rightarrow \sigma^*(\text{C–H}^a)$ electron delocalization (Scheme 81).¹¹⁵



Scheme 81.

Conversely, D. Lee suggested that carbene **198** would be expected to react preferentially with C–H^b to give **199**. Due to poor orbital overlap, the electron-delocalization $n(\text{O}) \rightarrow \sigma^*(\text{C–H}^a)$ would be diminished, leading the oxygen to inductively deactivate the C–H^a bond¹¹⁵ (Scheme 82).



Scheme 82.

In order to investigate this hypothesis, D. Lee designed two pairs of conformationally rigid diastereoisomers, **200a/200b** and **200c/200d**, which would mimic the insertion behaviour of **196** and **198** (Scheme 83). As expected **200a** underwent selective insertion into C–H^a, giving **201a**, with no evidence of **202a** observed. Allenylsilane **203a** was also observed as a significant by-product from the reaction. Conversely, **200b** gave a mixture of **201b** and **202b** in a 1:11 ratio, along with allenylsilane **203b**. The reaction of ketone **200c** gave a mixture of **201c** and **202c** in 1:5 ratio, while **200d** gave **202d** exclusively. Allenylsilanes **203c** and **203d** were also observed in these reactions.

The preferred formation of **202c** and **202d** through insertion into the apparently less activated C–H^b bond was deemed to be due to the stereoelectronic effect that D. Lee had previously proposed.¹¹⁵ The formation of allenylsilanes **203a–d** was thought to be due to an intermolecular process that occurs because of the lower reactivity of C–H bonds in conformationally constrained systems

compared with those in more flexible systems.^{115b} D. Lee was able to selectively synthesize these interesting functionalities by altering the reaction conditions (vide infra).

This work by D. Lee et al. has offered significant insight into the role played by oxygen in affecting the selectivity of 1,5 C–H insertion reactions, as well as addressing how various other subtle changes can drastically alter how this reactive intermediate will behave.

4.2. Effect of reaction conditions on selectivity

While significant changes in the selectivity of alkylidene carbenes can generally only be brought about through substrate modification, there have been reports where altering the reaction conditions under which the alkylidene carbene is generated have led to changes in selectivity. Gilbert reported that increasing the polarity of the solvent used for the reaction of **204** with **151**, resulted in an increase in the formation of alkyne **206** via migra-

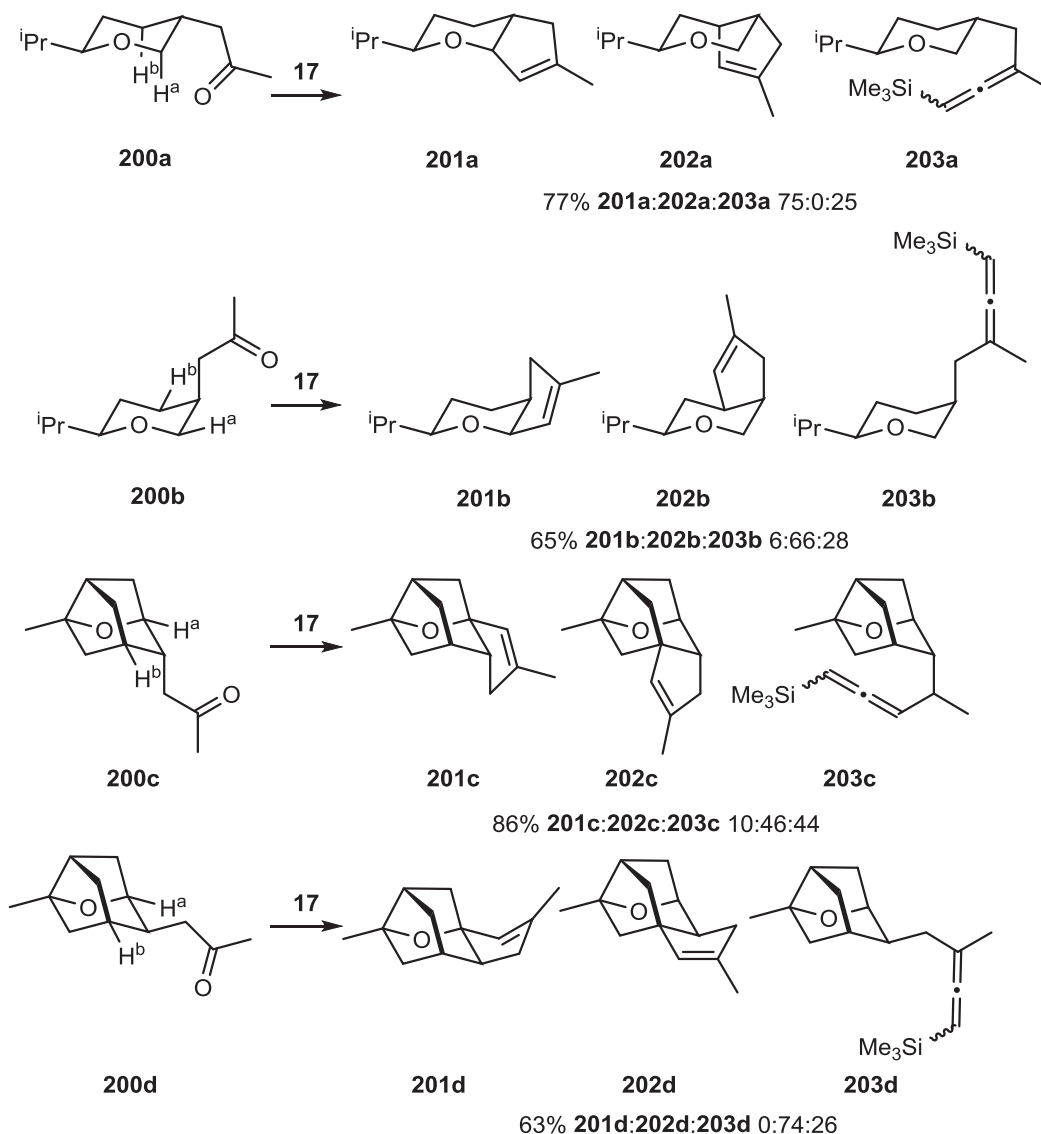
tion, compared to C–H insertion to form 3-pyrrol-2-one **205**, with an eventual reversal of selectivity occurring in water (Scheme 84).¹¹⁰

Taber demonstrated a similar change in chemoselectivity in a competition between N–H insertion and 1,2-aryl migration, the

ratio of which could be altered by changing the reaction solvent.¹¹⁶ Increasing the polarity of the solvent resulted in the increased formation of indole **208**, in comparison to alkyne **207**, when generating the alkylidene carbene from **206** (Scheme 85).

An earlier study by Garcia-Gabiray on alkyl carbenes suggested that less polar solvents could give rise to the triplet state, and thus differing reactivity.¹¹⁷ However, Taber believed that both **207** and **208** arose from the singlet alkylidene carbene and so suggested that the change in reactivity was more likely as a result of a solvent-induced change in the hybridization of the alkylidene carbene.

The effect of altering the solvent and temperature on alkylidene carbene selectivity was seen by Hayes while investigating the reaction of vinyl bromide **209** with KHMDS as a route to (+)-lactacystin (Scheme 86).¹¹⁸ The ratio of 1,5 C–H insertion to 1,2-migration increased by performing the reaction in THF instead of Et₂O. Further increases could be achieved by performing the reaction at lower temperatures.



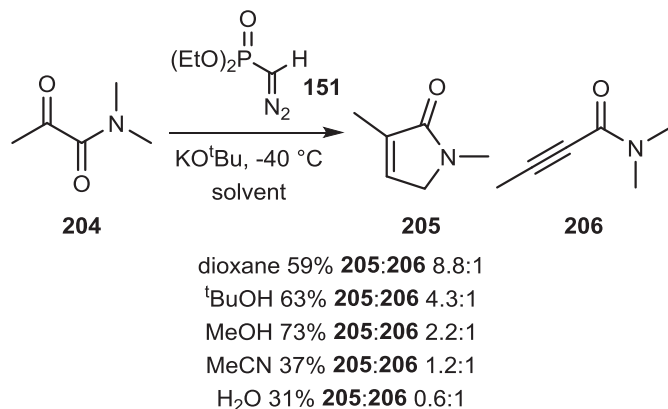
Scheme 83.

Wardrop had previously investigated the same reaction in his formal synthesis of (+)-lactacystin and described the ratio of products obtained was also dependant of the geometry of the starting vinyl bromide.¹¹⁹ Treating a mixture of (*E/Z*)-**209** with

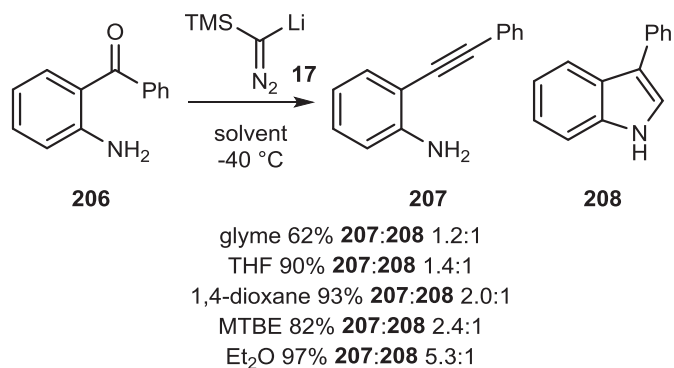
KHMDS in ether, gave a mixture of dihydropyrrole **210** and alkyne **211** in a ~1.4:1 ratio. However, when a pure sample of (*E*)-**209** was reacted under the same conditions the efficiency of the insertion reaction improved, giving the mixture of **210** and **211** in a ~2.7:1 ratio. Conversely, a pure sample of (*Z*)-**209** gave preferential formation of alkyne **211**, as a 3:1 mixture with **210**.¹¹⁹

The latter result is somewhat surprising as it has been shown that the alkene geometry has little effect on the efficiency of C–H insertion reactions.^{21a} Wardrop offered no explanation for this unusual phenomenon, however, subsequent work by D. Lee suggests that insertion into the desired C–H bond may be retarded due to the conformation rigidity of the dioxane system,¹¹⁵ coupled with the proximity of the bulky ^{*i*}Pr group, allowing the alkyne formation to compete. It remains unclear why the efficiency of this reaction should depend on the geometry of the starting vinyl bromide.

In 2012, Xi also demonstrated a profound change in reactivity when altering the solvent in which the reaction of dibromoalkenes with ^{*n*}BuLi was performed (Scheme 87).¹²⁰ When the reaction was carried out in hexane, the alkyne was formed via 1,2 aryl migration. However, when THF was used, the butatriene (mainly *E*) was



Scheme 84.

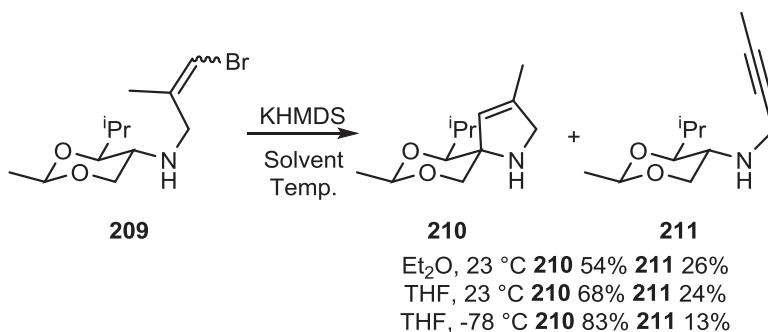


Scheme 85.

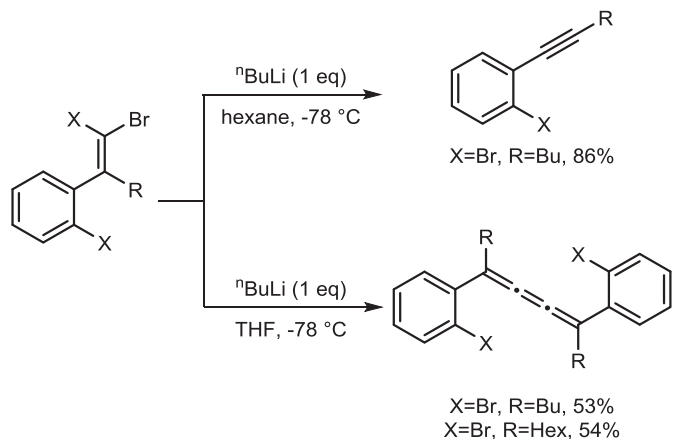
isolated, the product of dimerization of the intermediate alkylidene carbenoid.

Xi suggested that the difference in polarity and coordination ability of the solvents was responsible for this significant change in reactivity.¹²⁰

Taber reported an increase in the regioselectivity of 1,5 C–H insertion reactions by altering the manner in which the alkylidene carbene was generated.^{55a} Treating ketone **212** with TMSCHN₂ and MeLi resulted in a mixture of dihydrofuran **213** and cyclopentene **214**, with a slight preference for insertion into the primary C–H over the tertiary C–H. When the same ketone was converted to the vinyl chloride and treated with KHMDS, the ratio of **213** to **214** increased, again in favour of the dihydrofuran, in accordance with the increased activation effect seen from *endo* oxygen over *exo* oxygen (Scheme 88).



Scheme 86.

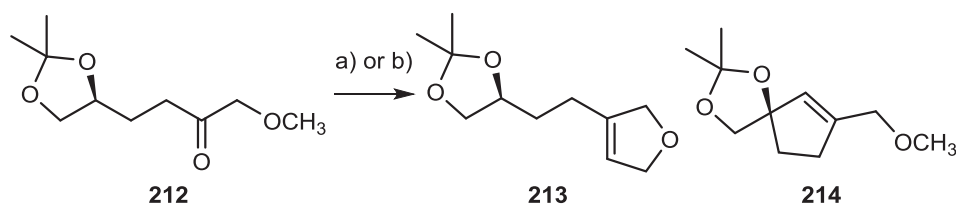


Scheme 87.

Taber suggested that carbenes generated via α -elimination are more carbenoid in nature, and their reactivity is tempered by the coordination of metal salts, resulting in increased regioselectivity in the C–H insertion reaction.

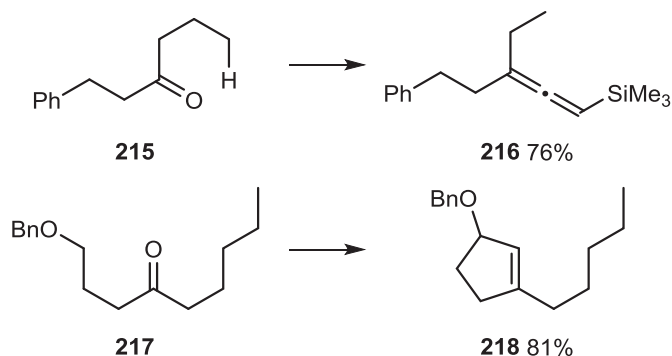
As has already been described (Scheme 83), D. Lee reported the formation of allenylsilanes in the reactions of substrates where the C–H required for insertion was relatively unreactive. By increasing the relative amount of TMSCHN₂ and ⁿBuLi in the reaction, as well as increasing the reaction concentration, D. Lee was able to form the allenylsilane preferentially. Hence the formation of **216** from **215** could be achieved in good yield, whereas **217** gave only the product of 1,5 C–H insertion due to the activating effect of the adjacent oxygen (Scheme 89).

D. Lee proposed that the allenylsilane arose from an intermolecular reaction between the alkylidene carbene **219** and trimethyldiazomethane to form **220**. Subsequent elimination of nitrogen would result in the formation of allenylsilane **221** (Scheme 90).



a) TMSCHN₂/MeLi, 60%, **213:214** 55:45
 b) Ph₃PCHCl then KHMDS, 93%, **213:214** 91:9

Scheme 88.

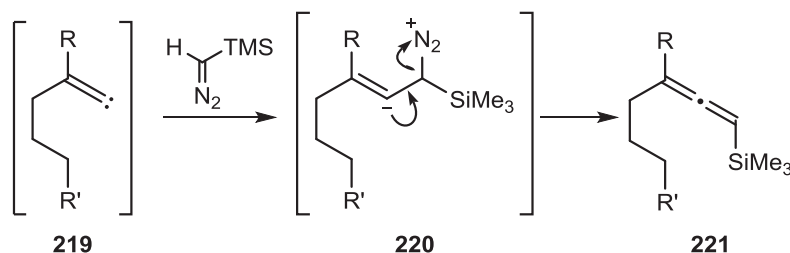


Scheme 89.

transition state **224**, with the methyl group in a pseudoequatorial position, was 1.5 kcal/mol lower in energy than **225**, resulting in the formation of the *anti*-isomer **222** being more favourable than the *syn* isomer **223**.⁷

Taber also reported 1,3 diastereomeric induction in the reaction of ketone **226** to form cyclopentenones **227** and **228** in a 2.4:1 ratio (Scheme 93).¹²³ The benzyl group was removed to give the natural product α -necrodol, and its *cis* diastereoisomer.¹²³

Taber proposed four possible transition states **230**–**233** for the 1,5 C–H insertion reaction (Fig. 7). Calculations (using an MM2 force field and a ‘weak bond’ between the carbenic atom and the H atom) showed that **230** and **231**, which would lead to the *trans* product, were lower in energy than either **232** or **233**, which would give the *cis* product. It is notable that **232**, with two pseudoequatorial substituents, is thought to be less stable than either **230** or

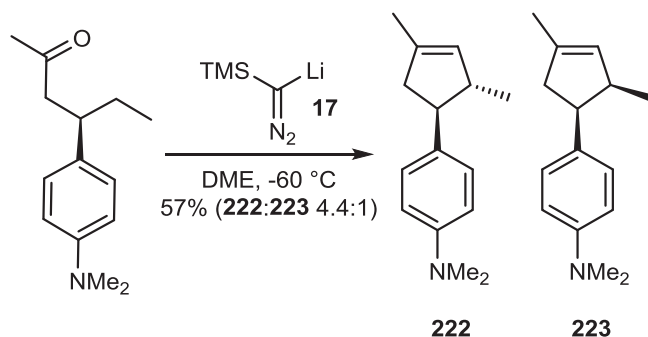


Scheme 90.

5. Diastereoselectivity

Alkylidene carbenes can sometimes undergo highly diastereoselective reactions, although the diastereoselectivity has not always been rationalized. Examples previously reported in this review include the formation of **53** (Scheme 19) and the 1,5 C–H insertion of alkylidene carbenoid **90** (Scheme 39).^{38,56} In the formation of fused bicyclic systems, the *cis* ring junction is usually formed,^{57a,b,112,113,115,121} however *trans* formation is clearly possible as seen in the formation of **176** (Scheme 78) and to some extent **201c** and **202c** (Scheme 83).^{112,115}

In 1994, Taber reported the first diastereoselective 1,5 C–H insertion reaction, synthesizing cyclopentenones **222** and **223** as a 4.4:1 mixture of diastereoisomers (Scheme 91).¹²²



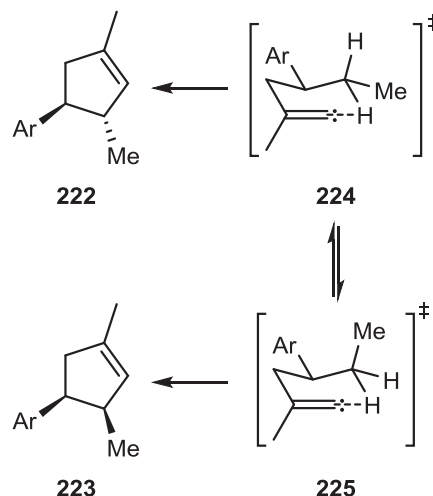
Scheme 91.

Taber proposed that this selectivity arose from more favourable interactions within the transition state of the insertion reaction (Scheme 92). It was calculated (using an MM2 force field and a ‘weak bond’ between the carbenic atom and the H atom) that

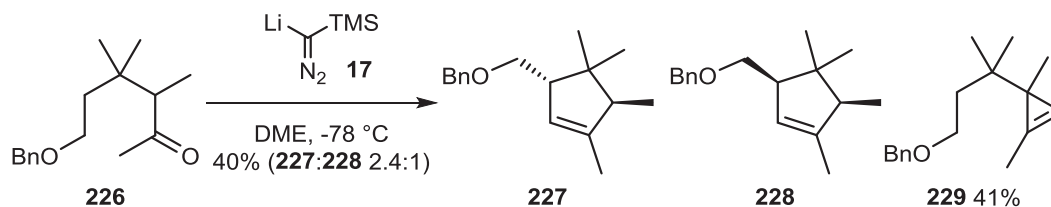
231, which each contain one pseudoaxial substituent. This is believed to be due to the increased *gauche* interactions in **232** between the *gem*-dimethyl group and both pseudoequatorial substituents.¹²³

Interestingly, the major product in the reaction above was cyclopropene **229**, the result of 1,3 C–H insertion (Scheme 93). Taber postulated that 1,5 C–H insertion would be retarded by the β -oxygen substituent, while 1,3 C–H insertion could be accelerated due to it being a tertiary C–H bond as opposed to the secondary C–H undergoing 1,5 C–H insertion, resulting in the cyclopropene being the major product.

Wills also reported 1,3-diastereomeric induction in the synthesis of dihydrofurans **235** and **236** from ketone **234** (Scheme 94).¹²⁴



Scheme 92.



Scheme 93.

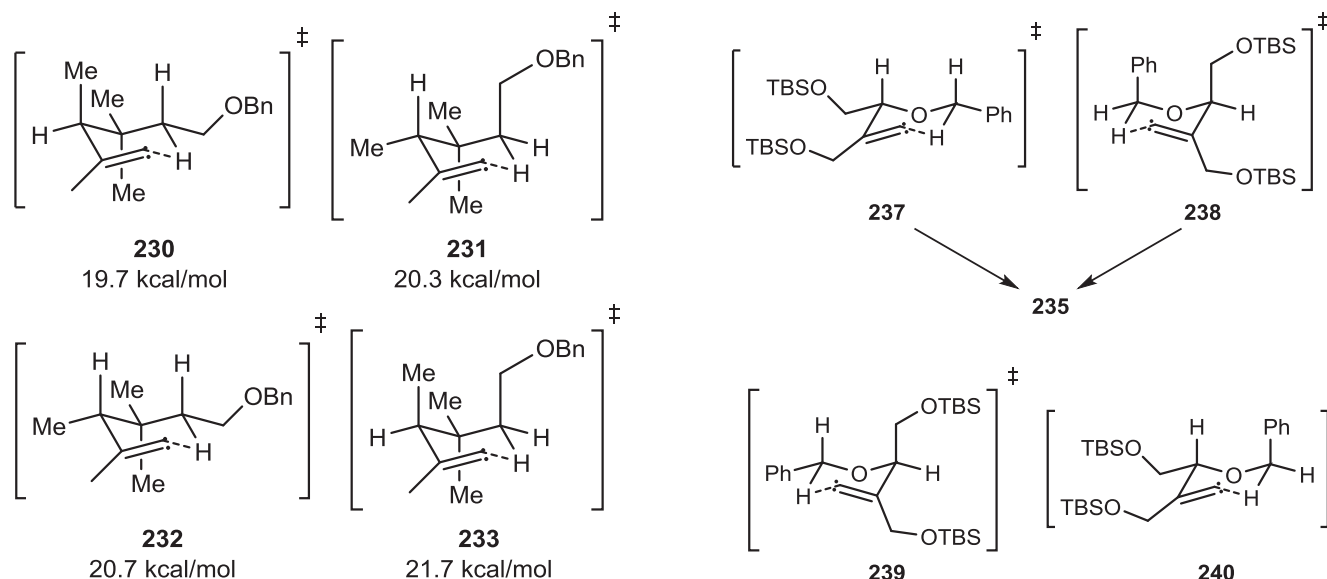


Fig. 7.

Proposing similar transition states **237**–**240** to Taber,^{7,123} Willis argued that the formation of **235** was more favourable due to the diminished steric interactions present in **237** by having both the CH_2OTBS and phenyl groups in pseudoequatorial positions (Fig. 8).¹²⁴

Van Nhien and Postel reported diastereoselective induction in 1,5 C–H insertion reactions on a sugar-derived system.^{9,125} Treatment of cyano mesylate **241** with TMSN_3 and Bu_2SnO gave trans isomer **242** as the major product (Scheme 95).⁹

Calculations (B3LYP with 6-31(d,p) basis set) showed the transition state leading to **243** was higher in energy by ~ 2.5 kcal/mol than the transition state leading to **242**, due to electrostatic repulsion between the dioxolane and benzoyl groups.⁹

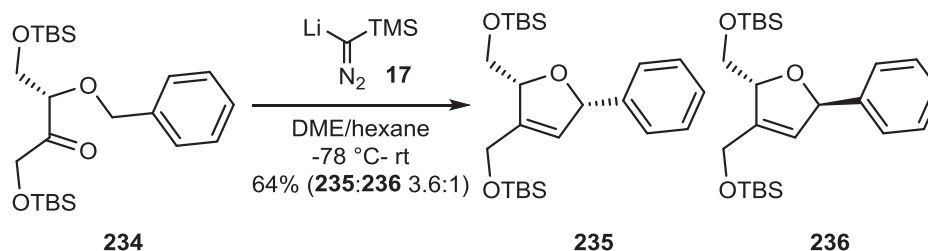
Treatment of sulfonamides **244** with base resulted in the bicyclic alkaloid skeleton **245**, via intramolecular nucleophilic attack on the alkynyl iodonium salt and subsequent 1,5 C–H insertion of the resulting alkylidene carbene (Scheme 96).^{57a}

The diastereoselectivity of the reaction was rationalized in terms of the transition state **246**,^{10,57a} where the steric interactions between the non-hydrogen group on C-5 and the rest of the molecule are minimized, leading to the major product (Scheme 97).

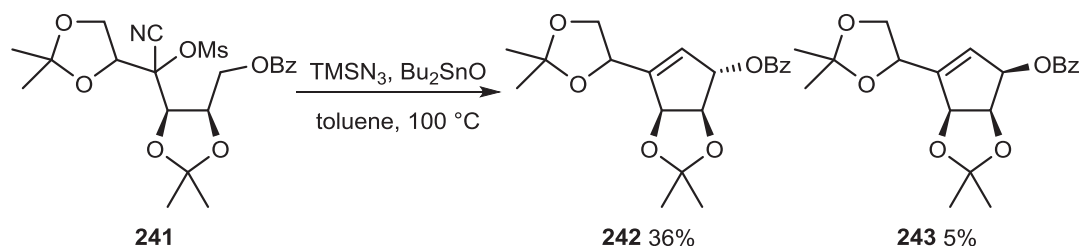
When the sulfonamides were replaced with alcohols, the resulting fused tetrahydrofurans were formed with higher diastereoselectivity (Scheme 98).^{57b}

Feldman argued that the alkylidene carbene generated in the oxygen system was less electrophilic than that in the nitrogen examples, due to the absence of the electron-withdrawing tosyl substituent, rendering it less reactive towards C–H insertion. This results in a later, more product-like transition state where the steric interactions would be more apparent, resulting in higher diastereoselectivity.

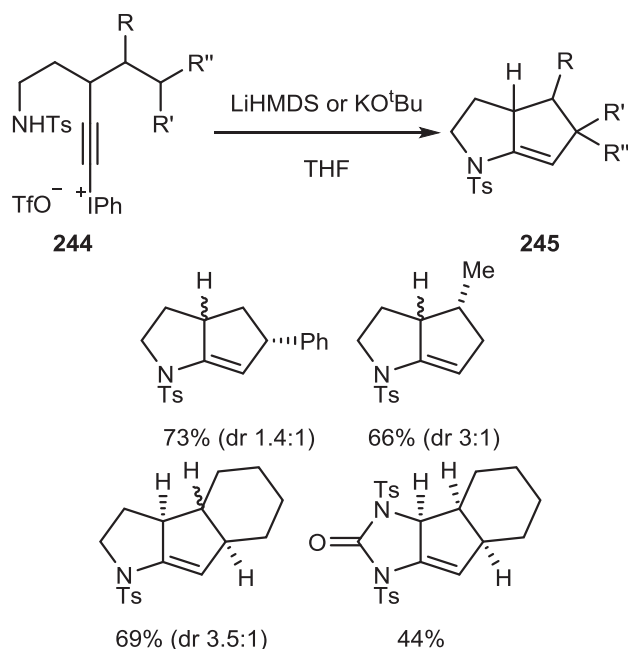
Grainger and Munro reported the first diastereotopic group selective 1,5 C–H insertion reactions of alkylidene carbenes, with the thermolysis of α,β -epoxy-*N*-aziridinylimine **247** giving a mixture of cyclopentenols **248** and **249** in a 2:1 ratio, with a preference for insertion into C–H^a (Scheme 99).^{55b} Protecting the tertiary alcohol as the silyl ether **250** reversed the observed selectivity, with insertion into C–H^b, to give **252**, preferred.



Scheme 94.



Scheme 95.



Scheme 96.

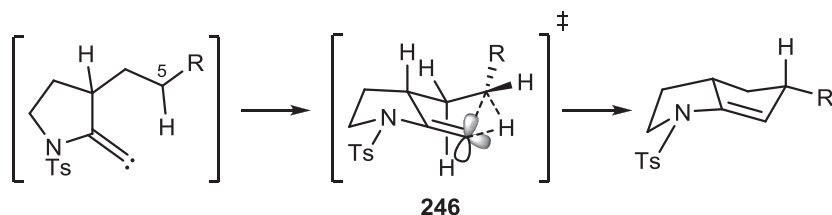
It was postulated that the diastereoselectivity arose from interactions within the newly formed vicinal diol (Scheme 100).^{55b} When the tertiary alcohol is unprotected, hydrogen bonding within the diol **253** would be expected to direct the alkylidene carbene towards reaction at C-H^a . Conversely, protecting the alcohol prevents this hydrogen bonding, and so steric repulsions between the silyl ether and the secondary alcohol promote insertion into the C-H^b bond.

These results demonstrate the sensitivity alkylidene carbenes have to the environment in which a C-H bond is located. The calculated energy differences between the transition states proposed by Taber, Van Nhlen and Postel are by no means excessive, and yet reasonable diastereoselectivities are obtained. Similarly, the work of Feldman and Grainger show have shown how relatively minor substrate modifications can have profound effects on diastereoselectivity in 1,5 C-H insertion reactions.

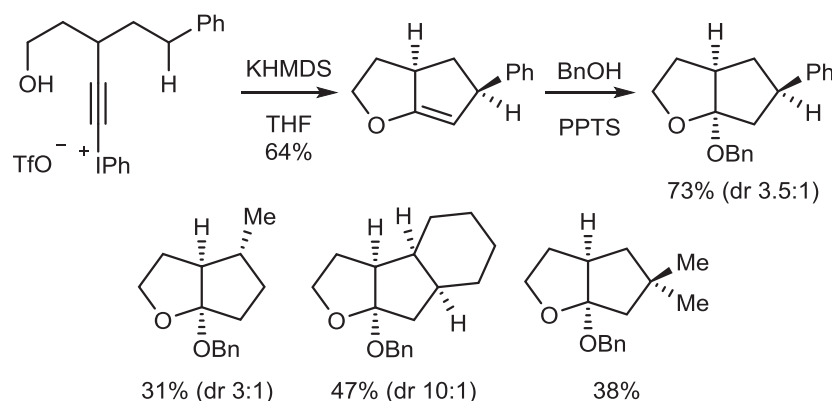
6. Alkylidene carbenes in target synthesis

Due to their versatility and ease of generation, coupled with their high levels of selectivity, alkylidene carbenes have seen widespread use in target synthesis, including natural products.^{2,7,21e,22,107c,121,126}

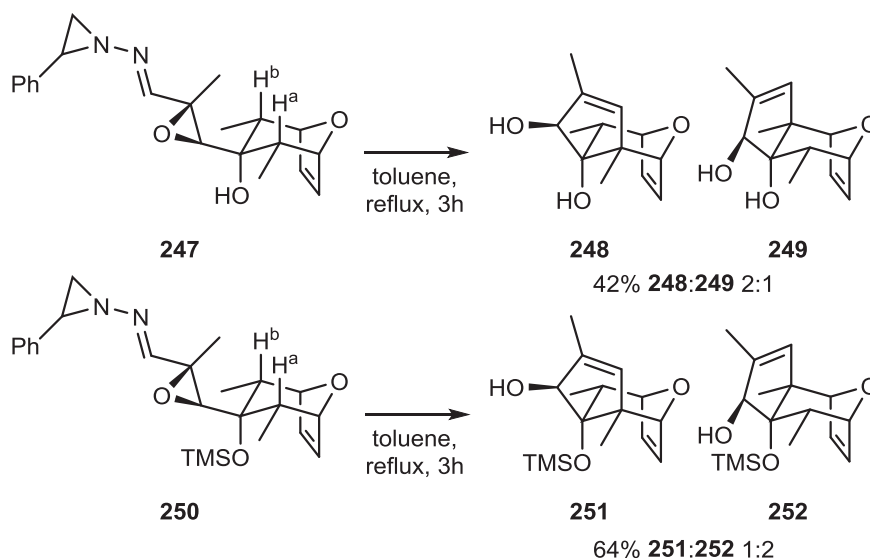
While the conversion of aldehydes to alkynes has not been discussed in detail in this review, it is nonetheless a powerful tool



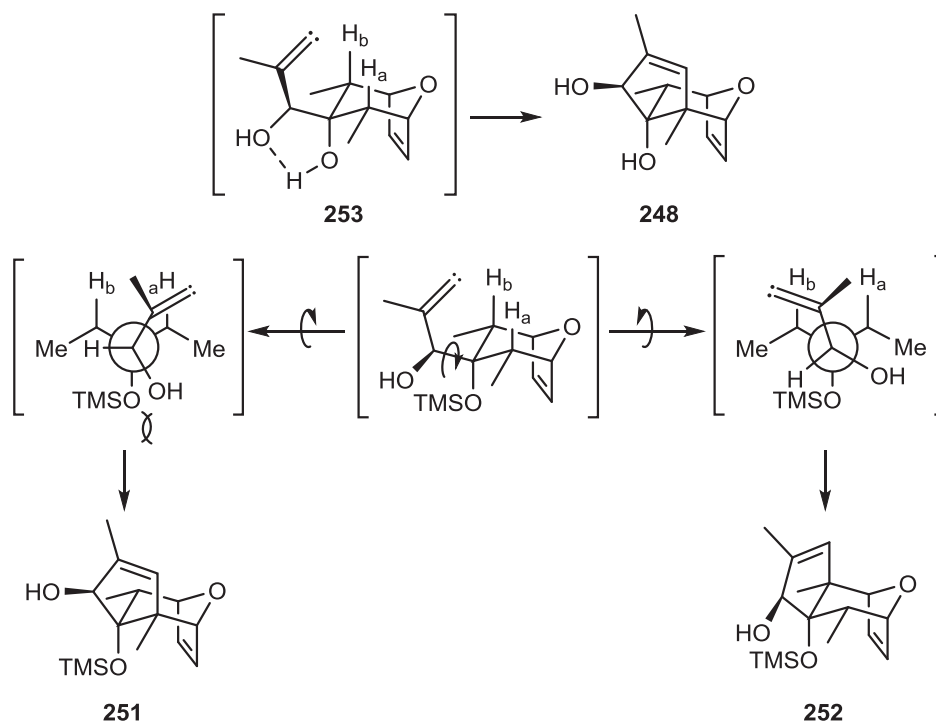
Scheme 97.



Scheme 98.



Scheme 99.



Scheme 100.

for the synthetic organic chemist.⁶ In particular, the Ohira–Bestmann reagent **254** (Fig. 9) has been utilized extensively in natural product synthesis. Li employed this reagent in the first total synthesis of (±)-δ-rubromycin, an anti-tumour compound (Scheme 101).¹²⁷

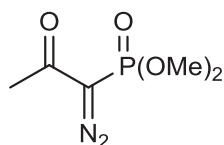
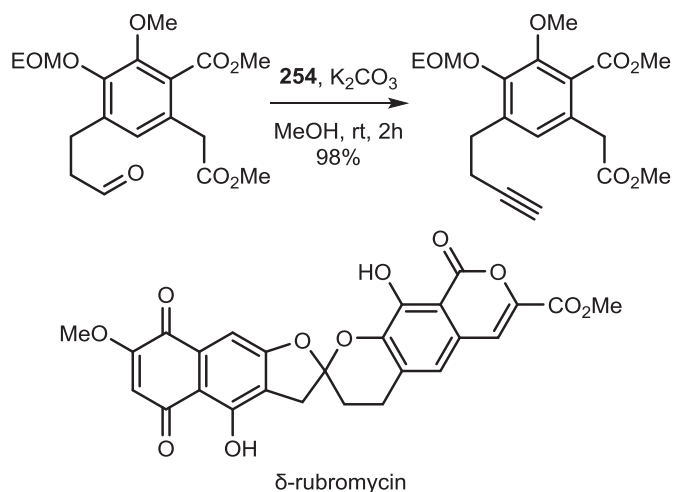


Fig. 9.

Similarly, Reddy utilized this transformation in the synthesis of oplopandiol, oploxyne A and (–)-oploxyne B (Scheme 102), all of which show activity towards a range of cancer cell lines.¹²⁸

The formation of cyclopentene rings via 1,5 C–H insertion reactions has also proven to be a useful transformation in target synthesis. Several approaches to nitrogen containing natural products utilizing the stereospecific 1,5 C–H insertion adjacent to nitrogen have been reported.^{21b,d,46,118,129} Hayes reported the synthesis of cyclopentene **256**, an intermediate in the formal syntheses of (–)-TAN1251A^{129a,h} and (–)-FR901483,^{129e} by treating vinyl chloride **255** with KHMDs (Scheme 103).

Hayes employed a related approach to the synthesis of another versatile intermediate for natural product synthesis. Reaction between ketone **257** and lithiated (trimethylsilyl)diazomethane gave



Scheme 101.

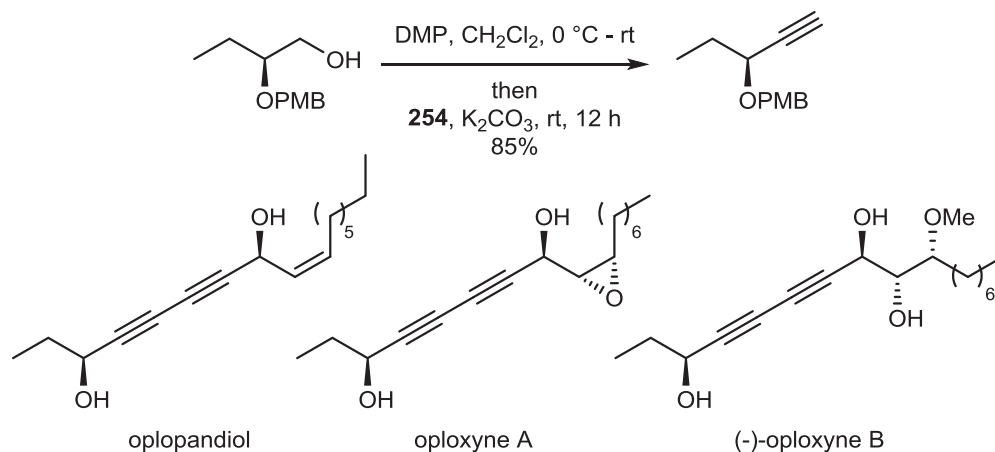
cyclopentene **258**, which was subsequently converted to several natural products including (1*S*,3*R*)-ACPD, (2*R*)-hydroxymethyl glutamic acid and (+)-lactacystin (Scheme 104).^{46,129b,i}

Hayes has utilized alkylidene carbene 1,5 C–H insertion reactions in the enantioselective syntheses of several other natural products including omuralide (and its C-7 epimer),¹¹⁸ and (–)-cephalotaxine.^{129f,g} An earlier approach to (+)-lactacystin, utilizing the 1,5 C–H insertion reaction of bromoalkene **209** (Scheme 86), was independently reported by Hayes¹¹⁸ and Wardrop.¹¹⁹

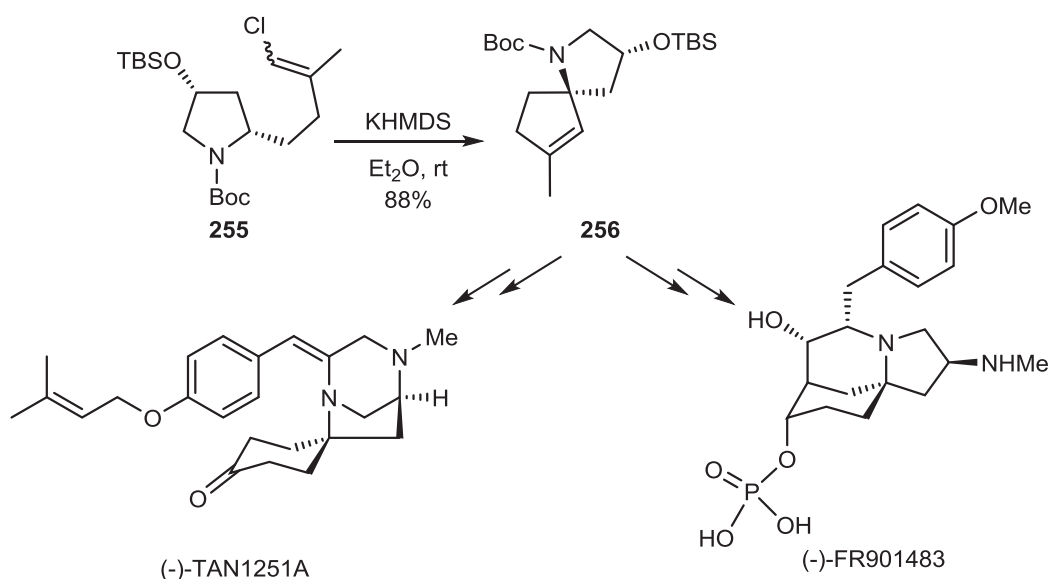
The reaction between alkynylidonium salts and soft nucleophiles has also been utilized in natural product synthesis,^{4d} particularly the use of sodium sulfonates as nucleophiles.^{76c,113,130} Wardrop employed this strategy in the synthesis of (±)-magnofargesin, a biologically active lignan (Scheme 105).^{76c}

While the above examples utilize the common generation methods and reactions of alkylidene carbenes in natural product synthesis, a number of alternative transformations have also been employed. Wardrop applied his tetraazafulvene methodology in a total synthesis of combretastatin A4 (Scheme 106).⁴¹

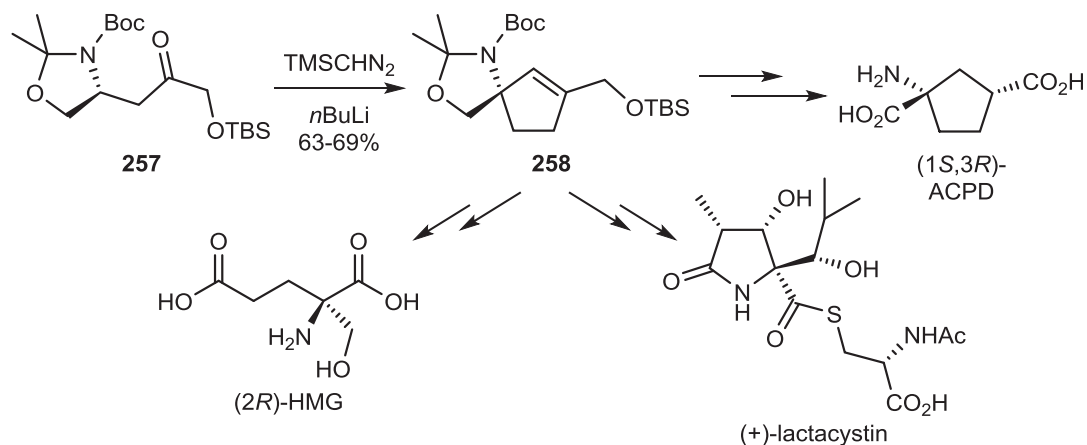
Tykwinski's demonstration that alkynyl groups undergo 1,2-migrations (Scheme 27)^{47,48,131} has led to significant developments in the synthesis of polyynes, and has been utilized in investigations



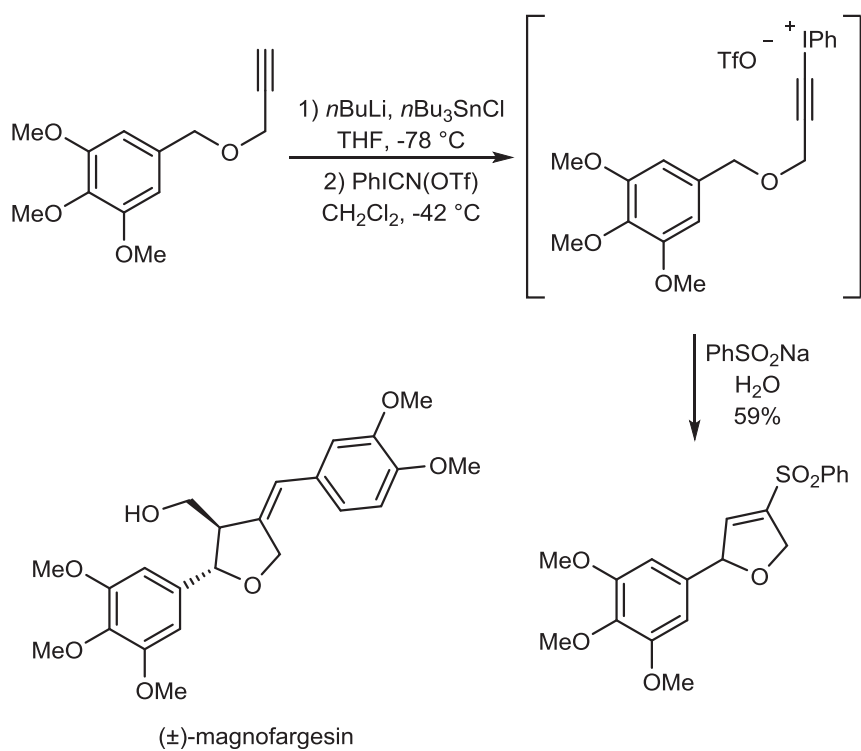
Scheme 102.



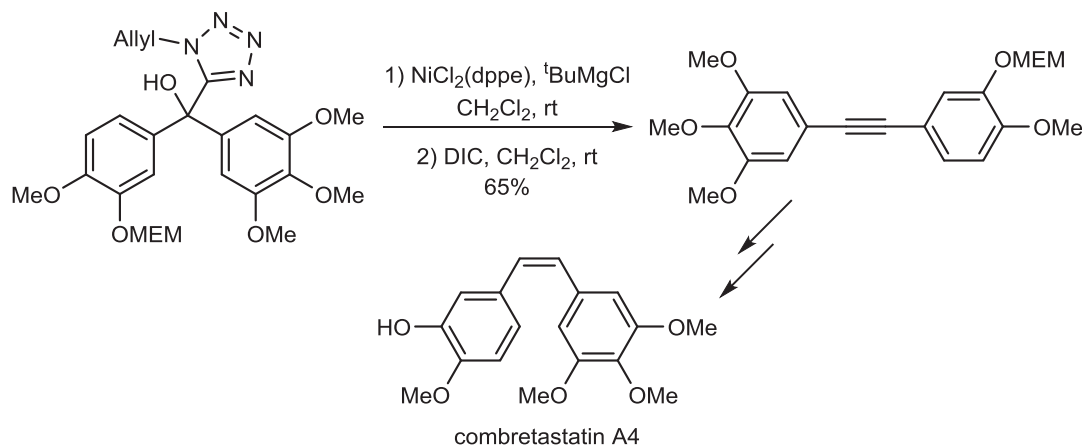
Scheme 103.



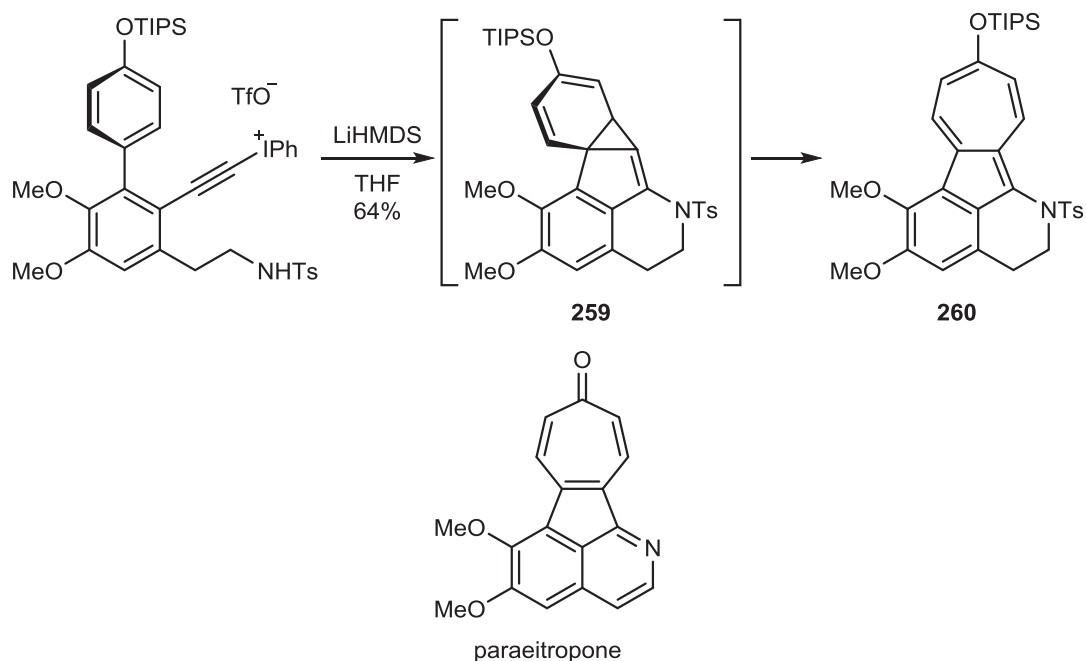
Scheme 104.



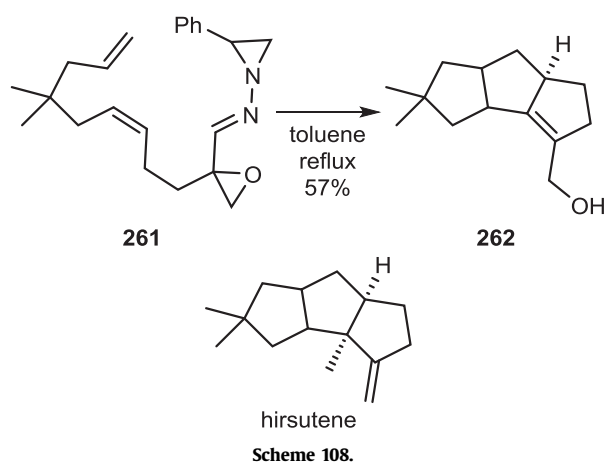
Scheme 105.



Scheme 106.



Scheme 107.



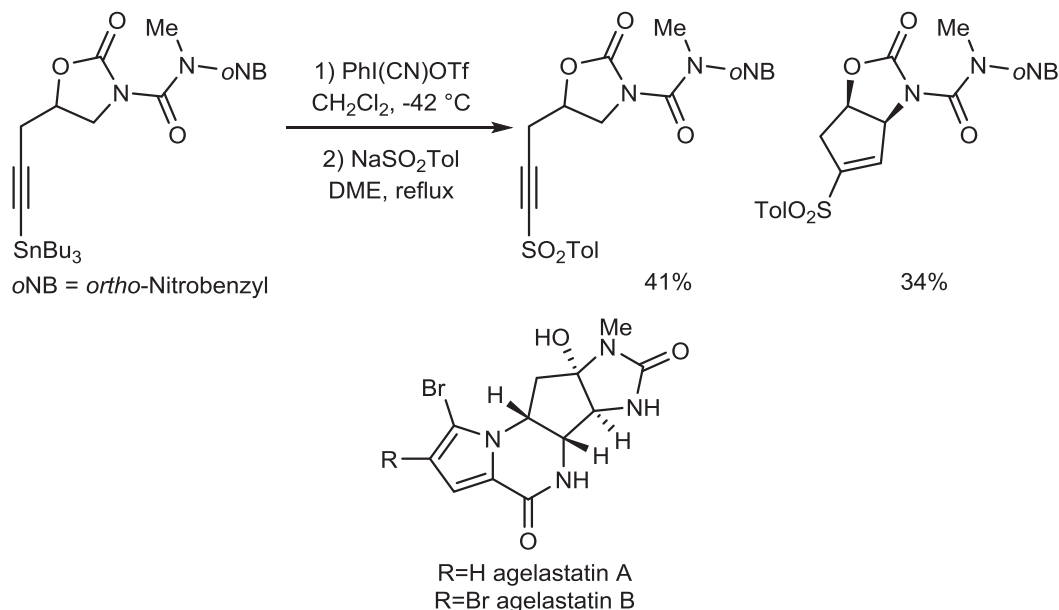
Scheme 108.

into the potential structure and properties of the proposed carbon allotrope carbyne.⁴⁹

The insertion of alkylidene carbenes into carbon–carbon double bonds has proven to be a useful tool in the synthesis of complex natural product frameworks. Feldman utilized this approach in the synthesis of paraeitropone, with the formation of polycycle **259** and subsequent ring expansion to **260** a key step in this synthesis (Scheme 107).^{130a,132}

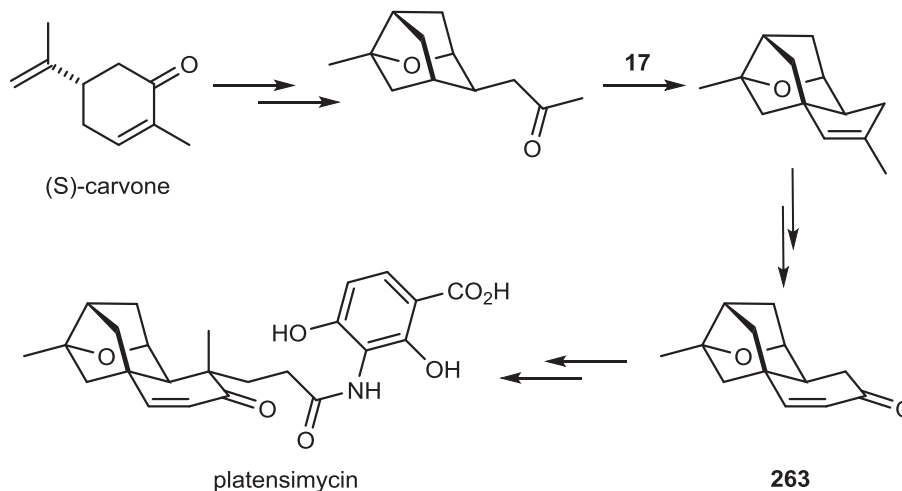
Similarly, H.-Y. Lee's conversion of α,β -epoxy-*N*-aziridinylimine **261** into triquinane **262** via the [2+1] cycloaddition, fragmentation and [3+2] cycloaddition process described previously (Scheme 12), was used in a synthesis of hirsutene (Scheme 108).^{30a}

In addition to the use of new alkylidene carbene reactions and generation techniques, increased knowledge of their selectivity has been exploited to achieve the synthesis of natural products. Feldman's study into the effects of the *N*-substituent (Scheme 79) was adapted for the total synthesis of (–)-agelastatin A and (–)-agelastatin B (Scheme 109).¹¹³



Scheme 109.

Likewise, D. Lee's comprehensive investigation into the effects of adjacent oxygen atoms on C–H insertion reaction allowed for a rapid synthesis of the tetracycle **263** from (*S*)-carvone,^{115a} a key intermediate in numerous total syntheses of platensimycin¹³³ (Scheme 110).



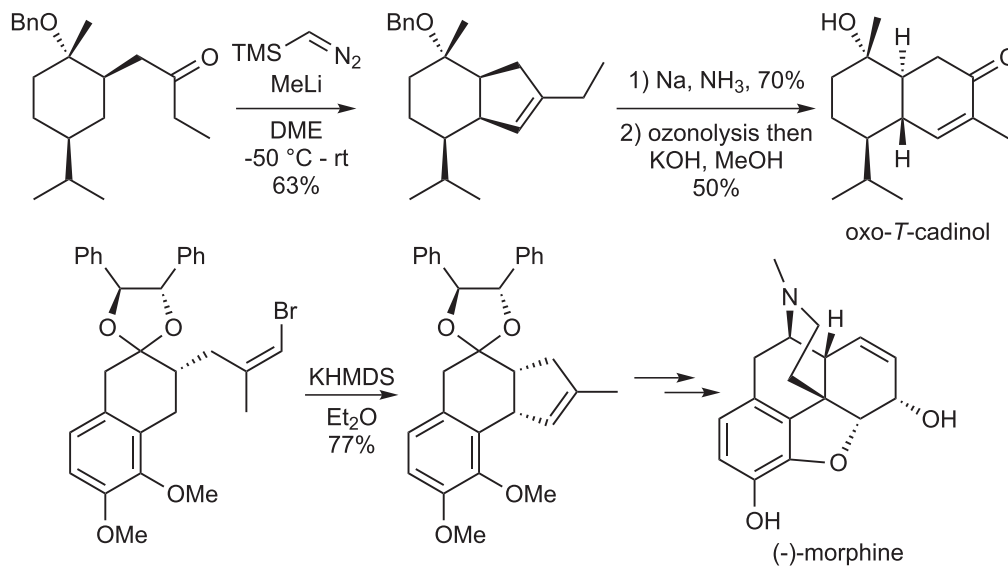
Scheme 110.

Taber has extensively utilized the stereospecific 1,5 C–H insertion reaction of alkylidene carbenes in natural product syntheses,^{7,21a,e,107c,121,123,126g,h,134} frequently exploiting the two-step transformation of the resulting cyclopentenones into cyclohexenones through oxidative cleavage followed by intramolecular aldol condensation and dehydration. Representative examples are in his syntheses of oxo-*T*-cadinol and (–)-morphine (Scheme 111).¹²¹ In

table recent breakthrough and suggests that catalytic asymmetric variants may be possible.

Acknowledgements

We thank the Engineering and Physical Sciences Research Council and University of Birmingham for funding our recent



Scheme 111.

both cases, *cis* [6,5] ring junctions are formed in the alkylidene carbene step, although *trans* formation is clearly possible, as described above.

studies on alkylidene carbenes.

7. Conclusions

The use of alkylidene carbenes in synthesis has reached a level where reasonable prediction can be made regarding

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